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NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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=> FIL REGISTRY
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
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Experimental and calculated property data are now available.  See HELP
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http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s cilostazol/cn
L1            1 CILOSTAZOL/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   73963-72-1  REGISTRY
CN   2(1H)-Quinolinone, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-
      (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Cilostazol
CN   Cilostazole
CN   OPC 13013
CN   OPC 21
CN   Pletaal
CN   Pletal
FS   3D CONCORD
DR   89332-50-3
MF   C20 H27 N5 O2
LC   STN Files:   ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN,
       CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE,
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       TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO
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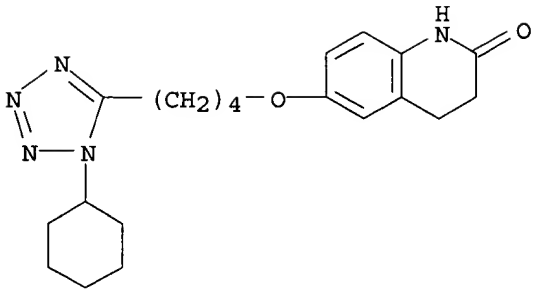

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

259 REFERENCES IN FILE CA (1962 TO DATE)
262 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> FIL MEDICINE
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L2        3451 L1 OR CILOSTAZOL? OR PLEETAL

=> s solub?
L3     1753055 SOLUB?

=> particle size or particle diameter
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L4      567871 PARTICLE SIZE OR PARTICLE DIAMETER

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L5          41 L2 AND L4

=> s l5 and l3
L6          30 L5 AND L3

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L7           23 DUP REM L6 (7 DUPLICATES REMOVED)

=> d l7 1-23 bib, ab, kwic

L7   ANSWER 1 OF 23  CAPLUS  COPYRIGHT 2002 ACS        DUPLICATE 1
AN   2002:185694  CAPLUS
DN   136:252483
TI   Clear oil-containing pharmaceutical compositions containing a therapeutic
     agent
IN   Chen, Feng-Jing; Patel, Mahesh V.; Fikstad, David T.
PA   USA
SO   U.S. Pat. Appl. Publ., 45 pp., Cont.-in-part of U.S. Ser. No. 751,968.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 4
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002032171	A1	20020314	US 2001-877541	20010608
	US 6267985	B1	20010731	US 1999-345615	19990630
	US 6309663	B1	20011030	US 1999-375636	19990817
	US 2001024658	A1	20010927	US 2000-751968	20001229
	US 6458383	B2	20021001		
PRAI	US 1999-345615	A2	19990630		
	US 1999-375636	A2	19990817		
	US 2000-751968	A2	20001229		
	WO 2000-US18807	A	20000710		

AB The present invention relates to pharmaceutical compns. and methods for improved **solubilization** of triglycerides and improved delivery of therapeutic agents. Compns. of the present invention include a carrier, where the carrier is formed from a combination of a triglyceride and at least 2 surfactants, at least one of which is hydrophilic. Upon diln. with an aq. medium, the carrier forms a clear, aq. dispersion of the triglyceride and surfactants. Thus, a formulation contained soybean oil, 80, Tween-20 200, and Tween-80 800 mg.

AB The present invention relates to pharmaceutical compns. and methods for improved **solubilization** of triglycerides and improved delivery of therapeutic agents. Compns. of the present invention include a carrier, where the carrier is formed from a combination of a triglyceride and at least 2 surfactants, at least one of which is hydrophilic. Upon diln. with an aq. medium, the carrier forms a clear, aq. dispersion of the triglyceride and surfactants. Thus, a formulation contained soybean oil, 80, Tween-20 200, and Tween-80 800 mg.

ST oil pharmaceutical triglyceride; **solubilization** oil pharmaceutical triglyceride surfactant

IT Antifoaming agents
Antioxidants
Buffers
Chelating agents
Compression
Encapsulation
Extrusion, nonbiological
Freeze drying
Granulation
Hydrophile-lipophile balance value
Lubricants
Particle size distribution
Peptidomimetics
Plasticizers
Preservatives
Surfactants
(clear oil-contg. pharmaceutical compns. contg. therapeutic agent)

IT 50-70-4, Sorbitol, biological studies 50-70-4D, Sorbitol, esters 50-78-2, Aspirin 56-81-5, Glycerol, biological studies 57-10-3, Palmitic acid, biological studies 57-11-4, Stearic acid, biological studies 57-55-6, Propylene glycol, biological studies 57-55-6D, 1,2-Propanediol, cyclodextrin ethers 58-32-2, Dipyridamole 58-95-7, .alpha.-Tocopherol acetate 59-02-9, .alpha.-Tocopherol 60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies 64-17-5, Ethanol, biological studies 67-63-0, Isopropanol, biological studies 77-89-4, Acetyl triethyl citrate 77-90-7, Acetyl tributyl citrate 77-93-0, Triethyl citrate 77-94-1, Tributyl citrate 81-24-3 81-25-4 81-81-2, Warfarin 83-44-3 87-69-4D, Tartaric acid, esters 87-78-5, Mannitol 100-51-6, Benzyl alcohol, biological studies 102-76-1, Triacetin 105-37-3, Ethyl propionate 105-54-4, Ethyl butyrate 105-60-2, .epsilon.-Caprolactam, biological studies 105-60-2D, .epsilon.-Caprolactam, derivs. 106-32-1, Ethyl caprylate 107-21-1, Ethylene glycol, biological studies 107-21-1D, Ethylene glycol, esters 107-88-0, 1,3-Butanediol 110-27-0, Isopropyl myristate 111-62-6, Ethyl oleate 111-90-0, Transcutol 112-80-1, Oleic acid, biological studies

115-77-5, Pentaerythritol, biological studies 115-77-5D, Pentaerythritol, esters 115-83-3, Pentaerythritol tetrastearate 118-71-8, Maltol 119-13-1, .delta.-Tocopherol 122-32-7, Glyceryl trioleate 124-07-2, Octanoic acid, biological studies 127-19-5, Dimethylacetamide 128-13-2 141-22-0 142-62-1, Hexanoic acid, biological studies 142-91-6, Isopropyl palmitate 143-07-7, Lauric acid, biological studies 148-03-8, .beta.-Tocopherol 151-41-7, Lauryl sulfate 334-48-5, Decanoic acid 360-65-6 434-13-9 463-40-1 474-25-9 475-31-0 490-23-3, .beta.-Tocotrienol 502-44-3, .epsilon.-Caprolactone 516-35-8 516-50-7 537-40-6, Glyceryl trilinoleate 538-23-8, Glyceryl tricaprylate 538-24-9, Glyceryl trilaurate 541-15-1D, Carnitine, esters with fatty acids, salts 544-35-4, Ethyl linoleate 544-63-8, Myristic acid, biological studies 555-43-1, Glyceryl tristearate 577-11-7, Sodium docusate 616-45-5, 2-Pyrrolidone 616-45-5D, 2-Pyrrolidone, derivs. 621-70-5, Glyceryl tricaproate 621-71-6, Glyceryl tricaprate 623-84-7, Propylene glycol diacetate 640-79-9 675-20-7, 2-Piperidone 675-20-7D, 2-Piperidone, derivs. 823-22-3, .delta.-Caprolactone 872-50-4, N-Methylpyrrolidone, biological studies 1331-12-0, Propylene glycol monoacetate 1338-39-2, Sorbitan monolaurate 1338-41-6, Sorbitan monostearate 1338-43-8, Sorbitan monooleate 1398-61-4, Chitin 1406-18-4, Vitamin E 1721-51-3, .alpha.-Tocotrienol 1935-18-8, Palmitoylcarnitine 2466-77-5, Lauroylcarnitine 2687-91-4, N-Ethylpyrrolidone 2687-94-7, N-Octylpyrrolidone 2687-96-9, N-Lauryl-2-pyrrolidone 3068-88-0, .beta.-Butyrolactone 3416-24-8, Glucosamine 3445-11-2 4345-03-3, .alpha.-Tocopherol succinate 5306-85-4, Dimethyl isosorbide 6493-05-6, Pentoxifylline 6990-06-3, Fusidic acid 7616-22-0, .gamma.-Tocopherol 7664-93-9D, Sulfuric acid, alkyl esters, salts 8007-43-0, Sorbitan sesquioleate 9002-89-5, Polyvinylalcohol 9002-92-0, Polyethylene glycol lauryl ether 9002-96-4 9003-39-8, Polyvinylpyrrolidone 9003-39-8D, PVP, conjugates with phosphatidylethanolamines 9004-34-6D, Cellulose, derivs. 9004-54-0, Dextran, biological studies 9004-57-3, Ethyl cellulose 9004-61-9, Hyaluronic acid 9004-65-3, Hydroxypropyl methyl cellulose 9004-67-5, Methyl cellulose 9004-74-4, Methoxy polyethylene glycol 9004-81-3, Polyethylene glycol monolaurate 9004-95-9, Polyethylene glycol cetyl ether 9004-96-0, Polyethylene glycol oleate 9004-98-2, Polyethylene glycol oleyl ether 9004-99-3, Polyethylene glycol monostearate 9005-00-9, Polyethylene glycol stearyl ether 9005-02-1, Polyethylene glycol dilaurate 9005-07-6, Polyethylene glycol dioleate 9005-08-7, Polyethylene glycol distearate 9005-25-8, Starch, biological studies 9005-32-7D, Alginic acid, salts 9005-37-2, Propylene glycol alginate 9005-49-6, Heparin, biological studies 9005-64-5, Polysorbate 20 9005-65-6, Polysorbate 80 9005-66-7, Tween 40 9005-67-8, Tween 60 9007-27-6, Chondroitin 9007-48-1, Polyglyceryl oleate 9009-32-9, Polyglyceryl stearate 9014-63-5, Xylan 9016-45-9, Polyethylene glycol nonyl phenyl ether 9041-08-1, Heparin sodium 9050-30-0, Heparan sulfate 9050-36-6, Maltodextrin 9062-73-1, Polyethylene glycol sorbitan laurate 9062-90-2, Polyethylene glycol sorbitan oleate 10041-19-7 11140-04-8, Imwitor 988 12619-70-4, Cyclodextrin 12619-70-4D, Cyclodextrin, hydroxypropyl ethers 12772-47-3, Pentaerythritol oleate 13027-26-4, .delta.-Tocopherol acetate 13081-97-5, Pentaerythritol distearate 13552-80-2, Glyceryl triundecanoate 14101-61-2, .gamma.-Tocotrienol 14440-80-3, Stearoyl-2 Lactylate 14465-68-0, Glyceryl trilinolenate 14605-22-2 22373-05-3, .beta.-Tocopherol acetate 22373-06-4, .gamma.-Tocopherol acetate 22882-95-7, Isopropyl linoleate 25168-73-4, Sucrose monostearate 25249-06-3, Polygalacturonic acid 25322-68-3D, ethers or esters 25322-69-4D, Polypropylene glycol, esters 25339-99-5, Sucrose monolaurate 25612-59-3, .delta.-Tocotrienol 25618-55-7D, Polyglycerol, esters with fatty acids 25637-97-2, Sucrose dipalmitate 26266-57-9, Sorbitan monopalmitate 26266-58-0, Sorbitan trioleate 26446-38-8, Sucrose monopalmitate 26658-19-5, Sorbitan tristearate 27195-16-0, Sucrose distearate 27321-96-6, Polyethylene glycol cholesteryl ether 29874-09-7, Myristoylcarnitine 29894-36-8, Polymannuronic acid

31692-85-0, Glycofurol 31694-55-0D, AMD triesters with fatty acids 35296-72-1, Butanol 36291-32-4, Citric acid monoglyceride 37270-89-6, Nadroparin calcium 51938-44-4, Sorbitan sesquistearate 53168-42-6, Myvacet 9-45 54392-26-6, Sorbitan monoisostearate 55142-85-3, Ticlid 56451-84-4 57307-93-4, Pentaerythritol caprylate 61725-93-7, Polyglyceryl distearate 61752-68-9, Sorbitan tetrastearate 64480-66-6, Glycoursodeoxycholic acid 68818-37-1, Pentaerythritol decanoate 68958-64-5, Polyethylene glycol glyceryl trioleate 69070-98-0 70226-44-7, Heparan **73963-72-1**, **Cilostazol** 74504-64-6, Polyglyceryl laurate 75634-40-1, Dermatan 83138-62-9, Polyglyceryl isostearate 88662-03-7 93790-70-6, Cholylsarcosine 93790-72-8, N-Methyltaurocholic acid 98913-68-9, Pentaerythritol isostearate 106392-12-5, Polyethylene glycol-polypropylene glycol block copolymer 110540-43-7, Polyglyceryl pentaoleate 113665-84-2, Clopidogrel 128254-89-7 128254-90-0 128286-20-4 146478-45-7, Polyglyceryl dioleate 148796-42-3 150372-93-3, Polyoxyethylene glyceryl laurate 162011-90-7, Rofecoxib 181695-72-7, Valdecoxib 198470-84-7, Parecoxib 208666-87-9, Captex 810D 256923-73-6, .gamma.-Tocotrienol acetate 300583-65-7 300583-68-0 403815-06-5 403815-07-6 403815-12-3 403821-12-5, Polyglyceryl trioleate 403838-29-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clear oil-contg. pharmaceutical compns. contg. therapeutic agent)

L7 ANSWER 2 OF 23 IFIPAT COPYRIGHT 2002 IFI DUPLICATE 2
AN 10155572 IFIPAT;IFIUDB;IFICDB
TI PROCESSES FOR PREPARING **CILOSTAZOL**
INF Finkelstein; Nina, Jerusalem, IL
Mendelovici; Marioara, Rehovot, IL
Pilarski; Gideon, Holon, IL
IN Finkelstein Nina (IL); Mendelovici Marioara (IL); Pilarski Gideon (IL)
PAF Unassigned
PA Unassigned Or Assigned To Individual (68000)
AG KENYON & KENYON, ONE BROADWAY, NEW YORK, NY, 10004, US
PI US 2002099213 A1 20020725
AI US 2001-929683 20010814
PRAI US 2000-190588P 20000320 (Provisional)
US 2000-225362P 20000814 (Provisional)
FI US 2002099213 20020725
DT Utility; Patent Application - First Publication
FS CHEMICAL
FS APPLICATION
CLMN 30
AB The present invention provides processes for preparing **cilostazol** and processes for purifying **cilostazol** by recrystallization.
TI PROCESSES FOR PREPARING **CILOSTAZOL**
AB The present invention provides processes for preparing **cilostazol** and processes for purifying **cilostazol** by recrystallization.
ECLM 1. A process for preparing **cilostazol** comprising: a) dissolving 6-hydroxy-3,4-dihydroquinolinone and a water-**soluble** base in water to form an aqueous phase, b) dissolving a 1-cyclohexyl-5(4-halobutyl)-tetrazole in a water-immiscible solvent to form an organic. . . the aqueous phase and the organic phase in the presence of a quaternary ammonium phase transfer catalyst, d) and recovering **cilostazol** from the biphasic mixture.
ACLM 7. The process of claim 1 wherein the water-**soluble** base is an alkali metal hydroxide, carbonate or bicarbonate.
8. The process of claim 7 wherein the water-**soluble** base is selected from the group consisting of NaOH, KOH, K2CO3, Na2CO3 and NaHCO3.
9. The process of claim 7 wherein the water-**soluble** base is NaOH.
12. A process for preparing **cilostazol** comprising: a) adding 6-hydroxy-3,4-dihydroquinolinone, a 1-cyclohexyl-5-(4-halobutyl)-

tetrazole, from about 0.9 to about 1.2 equivalents of an alkali metal hydroxide with respect. . . metal carbonate with respect to the dihydroquinolinone to a non-aqueous hydroxylic solvent to form a reaction mixture, and b) recovering **cilostazol** from the reaction mixture.
23. A process for preparing **cilostazol** comprising dissolving 6-hydroxy-3,4-dihydroquinolinone in a non-aqueous solvent, activating the phenol group of 6-hydroxy-3,4-dihydroquinolinone with an alkali metal hydroxide to form. . . byproduct of the phenol activation from the solvent by entrainment in molecular sieves, and thereafter adding a 1-cyclohexyl-5-(4-halobutyl)-tetrazole and recovering **cilostazol** from the solvent.
27. A process for purifying **cilostazol** by recrystallization from a solvent selected from the group consisting of 1-butanol, acetone, toluene, methyl ethyl ketone, dichloromethane, ethyl acetate,. . .
28. Highly pure **cilostazol** free of impurities.
29. Micronized **cilostazol** of small **particle size** and narrow **particle size** distribution.
30. Substantially pure **cilostazol** prepared by the process of any of claims 1, 12 and 23.

L7 ANSWER 3 OF 23 IFIPAT COPYRIGHT 2002 IFI DUPLICATE 3
AN 10069136 IFIPAT;IFIUDB;IFICDB
TI COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF LIPID REGULATING AGENTS; DRUG DELIVERY
INF Chen; Feng-Jing, Salt Lake City, UT, US
Patel; Mahesh V., Salt Lake City, UT, US
IN Chen Feng-Jing; Patel Mahesh V
PAF Unassigned
PA Unassigned Or Assigned To Individual (68000)
AG REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025, US
PI US 2002012680 A1 20020131
AI US 2001-898553 20010702
RLI US 1999-258654 19990226 CONTINUATION 6294192
FI US 2002012680 20020131
US 6294192
DT Utility; Patent Application - First Publication
FS CHEMICAL
FS APPLICATION
CLMN 140
GI 1 Figure(s).
FIG. 1 shows the enhanced bioabsorption of a hydrophobic therapeutic agent in the compositions of the present invention, relative to a commercial formulation.
AB The present invention relates to triglyceride-free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.
ACLM 33. The pharmaceutical composition of claim 1, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 100 nm.
34. The pharmaceutical composition of claim 33, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 50 nm.
35. The pharmaceutical composition of claim 33, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 20 nm.
38. The pharmaceutical composition of claim 1, wherein the hydrophobic therapeutic agent has an intrinsic water **solubility** of less

than about 1% by weight at 25 degrees C.
39. The pharmaceutical composition of claim 38, wherein the intrinsic water **solubility** is less than about 0.1% by weight at 25 degrees C.
40. The pharmaceutical composition of claim 39, wherein the intrinsic water **solubility** is less than about 0.01% by weight at 25 degrees C.
. . . ivermectin, amiodarone, zileuton, zafirlukast, albuterol, montelukast, azithromycin, ciprofloxacin, clarithromycin, dirithromycin, rifabutine, rifapentine, trovafloxacin, baclofen, ritanovir, saquinavir, nelfinavir, efavirenz, dicoumarol, tirofibran, **cilostazol**, ticlidopine, clopidrogel, oprevelkin, paroxetine, sertraline, venlafaxine, bupropion, clomipramine, miglitol, repaglinide, glymepride, pioglitazone, rosigiltazone, troglitazone, glyburide, glipizide, glibenclamide, carbamezepine, fosphenytion, tiagabine,. . .
49. The pharmaceutical composition of claim 1, which further comprises a **solubilizer**.
50. The pharmaceutical composition of claim 49, wherein the **solubilizer** is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.
54. The pharmaceutical composition of claim 49, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof,. . .
55. The pharmaceutical composition of claim 49, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol,. . .
56. The pharmaceutical composition of claim 49, wherein the **solubilizer** is triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycofurol,. . .
57. The pharmaceutical composition of claim 49, wherein the **solubilizer** is triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol or a mixture thereof.
58. The pharmaceutical composition of claim 49, wherein the **solubilizer** is present in the composition in an amount of about 400% or less by weight, based on the total weight. . .
59. The pharmaceutical composition of claim 58, wherein the **solubilizer** is present in the composition in an amount of about 200% or less by weight, based on the total weight. . .
60. The pharmaceutical composition of claim 59, wherein the **solubilizer** is present in the composition in an amount of about 100% or less by weight, based on the total weight. . .
62. The pharmaceutical composition of claim 60, wherein the **solubilizer** is present in the composition in an amount of about 50% or less by weight, based on the total weight. . .
62. The pharmaceutical composition of claim 61, wherein the **solubilizer** is present in the composition in an amount about 25% or less by weight, based on the total weight of. . .
. . . pharmaceutical composition of claim 1, which further comprises an additional amount of a hydrophobic therapeutic agent, said additional amount not **solubilized** in the carrier.
103. The pharmaceutical composition of claim 71, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 100 nm.
104. The pharmaceutical composition of claim 103, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 50 nm.
105. The pharmaceutical composition of claim 103, wherein the clear

aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 20 nm.

108. The pharmaceutical composition of claim 71, wherein the hydrophobic therapeutic agent has an intrinsic water **solubility** of less than about 1% by weight at 25 degrees C.

109. The pharmaceutical composition of claim 108, wherein the intrinsic water **solubility** is less than about 0.1% by weight at 25 degrees C.

110. The pharmaceutical composition of claim 109, wherein the intrinsic water **solubility** is less than about 0.01% by weight at 25 degrees C.

. . . ivermectin, amiodarone, zileuton, zafirlukast, albuterol, montelukast, azithromycin, ciprofloxacin, clarithromycin, dirithromycin, rifabutine, rifapentine, trovafloxacin, baclofen, ritanovir, saquinavir, nelfinavir, efavirenz, dicoumarol, tirofibran, **cilostazol**, ticlidopine, clopidrogel, oprevelkin, paroxetine, sertraline, venlafaxine, bupropion, clomipramine, miglitol, repaglinide, glymepride, pioglitazone, rosigiltazone, troglitazone, glyburide, glipizide, glibenclamide, carbamezepine, fosphenytion, tiagabine,. . .

119. The pharmaceutical composition of claim 71, which further comprises a **solubilizer**.

120. The pharmaceutical composition of claim 119, wherein the **solubilizer** is selected from the group consisting of alcohols, polyols, amides, esters, polyethylene glycol ethers and mixtures thereof.

124. The pharmaceutical composition of claim 119, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof,. . .

125. The pharmaceutical composition of claim 119, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol,. . .

126. The pharmaceutical composition of claim 119, wherein the **solubilizer** is triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycofurol,. . .

127. The pharmaceutical composition of claim 119, wherein the **solubilizer** is triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol or a mixture thereof.

128. The pharmaceutical composition of claim 119, wherein the **solubilizer** is present in the composition in an amount of about 400% or less by weight, based on the total weight. . .

129. The pharmaceutical composition of claim 128, wherein the **solubilizer** is present in the composition in an amount of about 200% or less by weight, based on the total weight. . .

130. The pharmaceutical composition of claim 129, wherein the **solubilizer** is present in the composition in an amount of about 100% or less by weight, based on the total weight. . .

131. The pharmaceutical composition of claim 130, wherein the **solubilizer** is present in the composition in an amount of about 50% or less by weight, based on the total weight. . .

132. The pharmaceutical composition of claim 131, wherein the **solubilizer** is present in the composition in an amount about 25% or less by weight, based on the total weight of. . .

. . . pharmaceutical composition of claim 71, which further comprises an additional amount of a hydrophobic therapeutic agent, said additional amount not **solubilized** in the carrier.

. . . dispersion of the hydrophilic and hydrophobic surfactants; (b) a first amount of a hydrophobic therapeutic agent, said first amount being **solubilized** in the carrier; and (c) a second amount of a hydrophobic therapeutic agent, said second amount not **solubilized**

in the clear aqueous dispersion, said composition being substantially free of triglycerides.

L7 ANSWER 4 OF 23 USPATFULL DUPLICATE 4
AN 2002:67175 USPATFULL
TI Administration of phosphodiesterase inhibitors for the treatment of premature ejaculation
IN Wilson, Leland F., Menlo Park, CA, UNITED STATES
Doherty, Paul C., JR., Cupertino, CA, UNITED STATES
Place, Virgil A., Kawaihae, HI, UNITED STATES
Smith, William L., Montclair, NJ, UNITED STATES
Abdel-Hamid Abdou Ali, Ibrahim AbouBakr, Mansoura, EGYPT
PI US 2002037828 A1 20020328
US 6403597 B2 20020611
AI US 2001-888250 A1 20010621 (9)
RLI Continuation-in-part of Ser. No. US 1999-467094, filed on 10 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1998-181070, filed on 27 Oct 1998, GRANTED, Pat. No. US 6037346 Continuation-in-part of Ser. No. US 1997-958816, filed on 28 Oct 1997, ABANDONED
DT Utility
FS APPLICATION
LREP REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
CLMN Number of Claims: 94
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 2011
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method is provided for treatment of premature ejaculation by administration of a phosphodiesterase inhibitor, e.g., an inhibitor of a Type III, Type IV, or Type V phosphodiesterase. In a preferred embodiment, administration is on as "as needed" basis, i.e., the drug is administered immediately or several hours prior to sexual activity. Pharmaceutical formulations and packaged kits are also provided.
DETD . . . imidazolines such as imazodan and 5-methyl-imazodan; imidazoquinoxalines; dihydropyridazinones such as indolidan and LY 81512 (5-(6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-1,3-dihydro-indol-2-one); dihydroquinolinone compounds such as cilostamide, **cilostazol**, vesnarinone, and OPC 3911 (N-cyclohexyl-N-hydroxymethyl-4-(2-oxo-1,2-dihydro-quinolin-6-yloxy)-butyramide); other compounds such as anagrelide, bemoradan, ibudilast, isomazole, lixazinone, motapizone, olprinone, phthalazinol, pimobendan, quazinone, siguazodan. . .
DETD . . . for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose and microcrystalline cellulose, as well as **soluble** materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride and sorbitol. Stabilizers are used to inhibit or retard drug. . .
DETD . . . inhibitor to be administered and any other components of the buccal dosage unit. Generally, the polymeric carrier comprises a hydrophilic (water-**soluble** and water-swellable) polymer that adheres to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include. . . one such polymer). Other suitable polymers include, but are not limited to: hydrolyzed polyvinylalcohol; polyethylene oxides (e.g., Sentry Polyox.RTM. water **soluble** resins, available from Union Carbide); polyacrylates (e.g., Gantre.RTM., which may be obtained from GAF); vinyl polymers and copolymers; polyvinylpyrrolidone; dextran;. . .
DETD . . . the like. Depending on the particular active agent, it may also be preferred that urethral suppositories contain one or more **solubilizing** agents effective to increase the **solubility** of the active agent in the PEG or other transurethral vehicle.
DETD [0100] Formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is **solubilized** in a carrier (e.g., propellant) or a dispersion aerosol in which the active agent is suspended or dispersed throughout a. . . thereof).

Non-aerosol formulations for inhalation may also comprise dry powder formulations, particularly insufflations in which the powder has an average **particle size** of about 0.1 .mu.m to 50 .mu.m, preferably 1 .mu.m to about 25 .mu.m.

DETD . . . Pharmacy, supra, at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-**soluble** bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable. . . water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-**soluble** ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy. . .

DETD [0106] Various additives, known to those skilled in the art, may be included in the topical formulations. For example, **solubilizers** may be used to **solubilize** certain active agents. For those drugs having an unusually low rate of permeation through the skin or mucosal tissue, it. . .

L7 ANSWER 5 OF 23 IFIPAT COPYRIGHT 2002 IFI
AN 3752608 IFIPAT;IFIUDB;IFICDB
TI COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF HYDROPHOBIC AGENTS
INF Chen; Feng-Jing, Salt Lake City, UT
Patel; Mahesh V., Salt Lake City, UT
IN Chen Feng-Jing; Patel Mahesh V
PAF Lipocine, Inc., Salt Lake City, UT
PA Lipocine Inc (57527)
EXNAM Page, Thurman K
EXNAM Channavajjala, Lakshmi
AG Reed, Dianne E.Reed & Associates
PI US 6451339 20020917
AI US 2001-898553 20010702
RLI US 1999-258654 19990226 CONTINUATION 6294192
FI US 6451339 20020917
US 6294192
DT UTILITY
FS CHEMICAL
FS GRANTED
CLMN 120
GI 1 Drawing Sheet(s), 1 Figure(s).

AB The present invention relates to triglyceride-free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.

ACLM 47. The formulation of claim 1, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 50 nm.
48. The formulation of claim 43, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 20 nm.
50. The formulation of claim 1, wherein the intrinsic water **solubility** is less than about 0.1% by weight at 25 degree(s) C.
51. The formulation of claim 47, wherein the intrinsic water **solubility** is less than about 0.01% by weight at 25 degree(s) C.
52. The formulation of claim 1, wherein the carrier further comprises a **solubilizer**.
53. The formulation of claim 52, wherein the **solubilizer** is selected from the group consisting of alcohols, polyols, amides, esters,

propylene glycol ethers and mixtures thereof.
54. The formulation of claim 53, wherein the **solubilizer** is an alcohol or polyol selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol,. . .
55. The formulation of claim 54, wherein the **solubilizer** is hydroxypropyl methylcellulose.
56. The formulation of claim 53, wherein the **solubilizer** is an amide selected from the group consisting of 2-pyrrolidone, 2-piperidone, epsilon -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, polyvinylpyrrolidone, and. . .
57. The formulation of claim 56, wherein the **solubilizer** is polyvinylpyrrolidone.
58. The formulation of claim 53, wherein the **solubilizer** is an ester selected from the group consisting of ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate,. . .
59. The formulation of claim 52, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof,. . .
60. The formulation of claim 52, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol,. . .
61. The formulation of claim 52, wherein the **solubilizer** is triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycofurol,. . .
62. The formulation of claim 52, wherein the **solubilizer** is triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol or a mixture thereof.
63. The formulation of claim 52, wherein the **solubilizer** is present in the composition in an amount of about 400% or less by weight, based on the total weight. . .
64. The formulation of claim 63, wherein the **solubilizer** is present in the composition in an amount of about 200% or less by weight, based on the total weight. . .
65. The formulation of claim 64, wherein the **solubilizer** is present in the composition in an amount of about 100% or less by weight, based on the total weight. . .
66. The formulation of claim 65, wherein the **solubilizer** is present in the composition in an amount of about 50% or less by weight, based on the total weight. . .
67. The formulation of claim 66, wherein the **solubilizer** is present in the composition in an amount about 25% or less by weight, based on the total weight of. . .
. . . 82. The formulation of claim 1, further comprising an additional amount of the lipid regulating agent, said additional amount not **solubilized** in the carrier.
100. The formulation of claim 98, wherein the anticoagulant is selected from the group consisting of **cilostazol**, clopidogrel, dicumarol, dipyridamole, nicoumalone, oprelvekin, phenindione, ticlopidine, aid tirofiban.
101. The formulation of claim 99, wherein the anticoagulant is selected from the group consisting of **cilostazol**, clopidogrel, dicumarol, dipyridamole, nicoumalone, oprelvekin, phenindione, ticlopidine, and tirofiban.

L7 ANSWER 6 OF 23 USPATFULL
AN 2002:199156 USPATFULL
TI EMULSION COMPOSITIONS FOR POLYFUNCTIONAL ACTIVE INGREDIENTS

IN CHEN, FENG-JING, SALT LAKE CITY, UT, UNITED STATES
PATEL, MAHESH V., SALT LAKE CITY, UT, UNITED STATES
PI US 2002107265 A1 20020808
AI US 1999-420159 A1 19991018 (9)
DT Utility
FS APPLICATION
LREP REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
CLMN Number of Claims: 100
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2236
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides pharmaceutical oil-in-water emulsions for delivery of polyfunctional active ingredients. The emulsions include an aqueous phase, an emulsifier, and an oil phase, wherein the oil phase includes a structured triglyceride that is substantially free of triglycerides having three C.sub.6-C.sub.12 fatty acid moieties, or a combination of a long chain triglyceride and a polarity-enhancing polarity modifier. The present invention also provides methods of treating an animal with a polyfunctional active ingredient, using dosage forms of the pharmaceutical emulsions.

SUMM [0008] Reportedly, such formulations enable better **solubilization** of polyfunctional active ingredients, compared to the less polar long chain triglycerides. See, e.g., Velazquez et al, "The scientific rationale. . .

SUMM . . . ingredients, particularly hydrophobic polyfunctional active ingredients. Unlike conventional formulations, the pharmaceutical emulsions of the present invention achieve effective and stable **solubilization** of the polyfunctional active ingredient without excessive amounts of organic solvents, hydrophilic synthetic surfactants, or medium chain fatty acid containing. . .

SUMM . . . the art that the term "lipophilic" means those members of the foregoing groups or classes of compounds which have significant **solubility** in oily solvents, and poor **solubility** in aqueous solvents. For compounds that can be characterized by a hydrophilic-lipophilic balance ("HLB") number, such as non-ionic compounds, lipophilic. . .

SUMM . . . acids and bases can be included in amounts sufficient to adjust the pH and/or the osmolality of the emulsion, the **solubility** of the polyfunctional active ingredient, the kinetic release profile, or other properties of the emulsion, as desired. In order to. . .

SUMM . . . an antiseptic, a buffering agent, a chelating agent, a colorant, a flavorant, an odorant, an osmotic modifier, a preservative, a **solubilizer**, a solvent, a tonicifier, a trace element, a viscomodulator, or a mixture thereof. Such additional additives can be present in. . .

SUMM . . . less than about 10. In another embodiment, the polyfunctional active ingredient is a hydrophobic active ingredient having an intrinsic aqueous **solubility** of less than about 1 mg/mL, preferably less than about 0.1 mg/mL. Of course, salts, isomers, derivatives, and mixtures of. . .

SUMM . . . ivermectin, amiodarone, zileuton, zafirlukast, albuterol, montelukast, azithromycin, ciprofloxacin, clarithromycin, dirithromycin, rifabutine, rifapentine, trovafloxacin, baclofen, ritanovir, saquinavir, nelfinavir, efavirenz, dicoumarol, tirofibran, **cilostazol**, ticlidopine, clopidrogel, oprevelkin, paroxetine, sertraline, venlafaxine, bupropion, clomipramine, miglitol, repaglinide, glymepride, pioglitazone, rosigiltazone, troglitazone, glyburide, glipizide, glibenclamide, carbamezepine, fosphenytion, tiagabine,. . .

SUMM . . . desired temperature. To further increase the load of the polyfuctional active or to facilitate the process, the active can be **solubilized** in an appropriate solvent or mixture of solvents prior to adding active to the oil phase. The solvents used in. . .

SUMM . . . 20 microns. The resulting mixture is further homogenized at a

desired pressure in batch-wise or continuous cycles until the desired **particle size** is obtained, typically a submicron **particle size**. Several high pressure homogenizers are available for this process, including EmulsiFlex (Avestin), microfluidizer (Microfluidics), and Rannie homogenizer (APV). The resulting. . .

SUMM [0069] Preferred emulsions can have a mean **particle diameter** of less than about 5 .mu.m, preferably less than about 2 .mu.m, more preferably less than about 1 .mu.m, still more preferably less than about 0.5 .mu.m, and most preferably less than about 0.3 .mu.m. **Particle size** can be determined by conventional methods, such as by measurement with a **particle size** analyzer.

SUMM . . . pharmaceutical emulsions described herein. The dosage form can be the pharmaceutical emulsion processed by lyophilization, encapsulation, extrusion, homogenization, sonication, melting, **solubilizing**, evaporation, mixing, coating, size reduction, spraying, sterilization, filtration, irradiation, or a combination thereof It should be appreciated that the ability. . .

SUMM . . . long chain triglyceride-based emulsion formulations, and more stable than medium chain-based emulsions. Structured triglycerides are believed to have a higher **solubilizing** potential for polyfunctional hydrophobic actives than do long chain triglycerides alone. The presence of shorter chain fatty acid groups makes the structured triglyceride more polar than long chain triglycerides, but not so polar as to negatively affect drug **solubility** and product stability, as is believed to be the case with medium chain triglycerides. These stable, higher drug loading formulations. . .

SUMM . . . oil phase as a result of the interactions with the polarity modifiers. Consequently, the circulating half-time of typical low-molecular weight water-**soluble** compounds can frequently be prolonged significantly. This will enable these actives to circulate and accumulate to an effective level at. . .

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 300 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 200 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 300 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 200 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 150 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 100 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a Branson sonifier. The pooled sonified material was then high

pressure homogenized as previously described. The resulting emulsion had mean **particle diameter** of less than 80 nm.

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 100 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 150 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 100 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 100 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.). 22

DETD . . . a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean **particle diameter** of less than 100 nm, as measured by a Nicomp **particle size** analyzer (**Particle Size** Systems, Inc.).

CLM What is claimed is:

3. The pharmaceutical emulsion of claim 2, wherein the polyfunctional active ingredient is hydrophobic and has an intrinsic aqueous **solubility** of less than about 1 mg/mL.

4. The pharmaceutical emulsion of claim 2, wherein the polyfunctional active ingredient is hydrophobic and has an intrinsic aqueous **solubility** of less than about 0.1 mg/mL.

. . . an antiseptic, a buffering agent, a chelating agent, a colorant, a flavorant, an odorant, an osmotic modifier, a preservative, a **solubilizer**, a solvent, a tonicifier, a trace element, a viscomodulator, or a mixture thereof.

. . . ivermectin, amiodarone, zileuton, zafirlukast, albuterol, montelukast, azithromycin, ciprofloxacin, clarithromycin, dirithromycin, rifabutine, rifapentine, trovafloxacin, baclofen, ritanovir, saquinavir, nelfinavir, efavirenz, dicoumarol, tirofibran, **cilostazol**, ticlidopine, clopidrogel, oprevelkin, paroxetine, sertraline, venlafaxine, bupropion, clomipramine, miglitol, repaglinide, glymepride, pioglitazone, rosigiltazone, troglitazone, glyburide, glipizide, glibenclamide, carbamezepine, fosphenytion, tiagabine,. . .

. . . form of claim 43, wherein the dosage form comprises the pharmaceutical emulsion processed by lyophilization, encapsulation, extrusion, homogenization, sonication, melting, **solubilizing**, evaporation, sterilization, filtration, irradiation, mixing, coating, size reduction, spraying, or a combination thereof.

73. The pharmaceutical emulsion of claim 72, wherein the polyfunctional active ingredient is hydrophobic and has an intrinsic aqueous **solubility** of less than about 1 mg/mL.

74. The pharmaceutical emulsion of claim 72, wherein the polyfunctional active ingredient is hydrophobic and has an intrinsic aqueous **solubility** of less than about 0.1 mg/mL.

. . . an antiseptic, a buffering agent, a chelating agent, a colorant, a

flavorant, an odorant, an osmotic modifier, a preservative, a **solubilizer**, a solvent, a tonicifier, a trace element, a viscomodulator, or a mixture thereof

IT 60142-96-3, Gabapentin 61270-78-8, Cefonicid sodium 61361-72-6, Dimyristoylphosphatidyl glycerol 61379-65-5, Rifapentine 61489-71-2, Menotropin 61869-08-7, Paroxetine 62013-04-1, Dirithromycin 62356-64-3 62893-19-0, Cefoperazone 63527-52-6, Cefotaxime 63585-09-1, Foscarnet sodium 63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 64228-81-5, Atracurium besylate 64544-07-6, Cefuroxime axetil 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 66376-36-1, Alendronate 66419-50-9, Bovine growth hormone 68099-86-5, Bepridil hydrochloride 68401-81-0, Ceftizoxime 68506-86-5, Vigabatrin 69049-74-7, Nedocromil sodium 69655-05-6, Didanosine 69756-53-2, Halofantrine 70288-86-7, Ivermectin 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 71486-22-1, Vinorelbine 72432-03-2, Miglitol 72559-06-9, Rifabutine 73384-59-5, Ceftriaxone 73590-58-6, Omeprazole **73963-72-1**, Cilostazol 74011-58-8, Enoxacin 74103-06-3, Ketorolac 74356-00-6, Cefotetan disodium 74381-53-6, Leuprolide acetate 75706-12-6, Leflunomide 76420-72-9, Enalaprilat 76470-66-1, Loracarbef 76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine 78110-38-0, Aztreonam 79350-37-1, Cefixime 79517-01-4, Octreotide acetate 79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9, Simvastatin 81093-37-0, Pravastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 81161-17-3, Esmolol hydrochloride 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 82626-48-0, Zolpidem 82952-64-5, Trimetrexate glucuronate 83799-24-0, Fexofenadine 83869-56-1, Granulocyte-macrophage colony stimulating factor 83881-51-0, Cetirizine 83905-01-5, Azithromycin 84057-84-1, Lamotrigine 84371-65-3, Mifepristone 84449-90-1, Raloxifene 84625-61-6, Itraconazole 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril 87679-37-6, Trandolapril 88669-04-9, Trospectomycin 89778-26-7, Toremifene 89987-06-4, Tiludronate 90357-06-5, Bicalutamide 91161-71-6, Terbinafine 93390-81-9, Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 94749-08-3, Salmeterol xinafoate 95233-18-4, Atovaquone 97240-79-4, Topiramate 97322-87-7, Troglitazone 97682-44-5, Irinotecan 98079-51-7, Lomefloxacin 98319-26-7, Finasteride 100986-85-4, Levofloxacin 101828-21-1, Butenafine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104227-87-4, Famciclovir 104987-11-3, Tacrolimus 105462-24-6, Risedronic acid 106133-20-4, Tamsulosin 106650-56-0, Sibutramine 106819-53-8, Doxacurium chloride 106861-44-3, Mivacurium chloride 107648-80-6, Cefepime hydrochloride 107753-78-6, Zafirlukast 110871-86-8, Sparfloxacin 111025-46-8, Pioglitazone 111406-87-2, Zileuton 112965-21-6, Calcipotriene 113189-02-9, Antihemophilic factor 113665-84-2, Clopidogrel 113852-37-2, Cidofovir 115103-54-3, Tiagabine 116094-23-6, Insulin aspart 117976-89-3, Rabeprazole 118072-93-8, Zoledronate 118292-40-3, Tazarotene 119914-60-2, Grepafloxacin 120014-06-4, Donepezil 121368-58-9, Olpadronate 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan 124832-26-4, Valaciclovir 127759-89-1, Lobucavir 127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1, Paricalcitol 133040-01-4, Eprosartan 133107-64-9, Insulin lispro 134523-00-5, Atorvastatin 134678-17-4, Lamivudine 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan 139110-80-8, Zanamivir 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 139639-23-9, Tissue type plasminogen activator 143003-46-7, Alglucerase 143011-72-7, Granulocyte colony stimulating factor 144034-80-0, Rizatriptan 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 145941-26-0, Oprelvekin 146961-76-4, Alatrofloxacin 147059-72-1, Trovafloxacin 148553-50-8, Pregabalin 151126-32-8, Pramlintide 153559-49-0, Targretin 154361-50-9,

Capecitabine 154598-52-4, Efavirenz 155213-67-5, Ritonavir 156259-68-6, Capmul MCM 157810-81-6, Indinavir sulfate 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir 160337-95-1, Insulin glargine 162011-90-7, Rofecoxib 165101-51-9, Becaplermin 169148-63-4, Insulin detemir 169590-42-5, Celecoxib 173146-27-5, Denileukin diftitox 191588-94-0, TNK-tPA 208666-87-9, Captex 810D
(oil-in-water emulsion compns. for polyfunctional active ingredients)

L7 ANSWER 7 OF 23 USPATFULL
AN 2002:191152 USPATFULL
TI Diagnostic/therapeutic agents
IN Klaveness, Jo, Oslo, NORWAY
Rongved, Pal, Oslo, NORWAY
Hogset, Anders, Oslo, NORWAY
Tolleshaug, Helge, Oslo, NORWAY
Naevestad, Anne, Oslo, NORWAY
Hellebust, Halldis, Oslo, NORWAY
Hoff, Lars, Oslo, NORWAY
Cuthbertson, Alan, Oslo, NORWAY
Lovhaug, Dagfinn, Oslo, NORWAY
Solbakken, Magne, Oslo, NORWAY
PA NYCOMED IMAGING AS (non-U.S. corporation)
PI US 2002102215 A1 20020801
AI US 2001-765614 A1 20010122 (9)
RLI Continuation of Ser. No. US 1997-960054, filed on 29 Oct 1997, PATENTED
Continuation-in-part of Ser. No. US 1997-958993, filed on 28 Oct 1997, PATENTED
PRAI GB 1996-22366 19961028
GB 1996-22367 19961028
GB 1996-22368 19961028
GB 1997-699 19970115
GB 1997-8265 19970424
GB 1997-11842 19970606
GB 1997-11846 19970606
US 1997-49264P 19970606 (60)
US 1997-49265P 19970606 (60)
US 1997-49268P 19970607 (60)
DT Utility
FS APPLICATION
LREP BACON & THOMAS, PLLC, 4th Floor, 625 Slaters Lane, Alexandria, VA, 22314-1176
CLMN Number of Claims: 37
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 6583
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, having reporters comprising gas-filled microbubbles stabilized by monolayers of film-forming surfactants, the reporter being coupled or linked to at least one vector.
DETD . . . or ionic bonds, or may be physically mixed into the stabilising material, particularly if the drug has similar polarity or **solubility** to the membrane material, so as to prevent it from leaking out of the product before it is intended to. . .
DETD . . . be employed; linking may be facilitated through addition of an amine or may result in direct vector-receptor coupling. Useful water **soluble** carbodiimides include 1-cyclohexyl-3-(2-morpholinyl-4-ethyl)carbodiimide (CMC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), e.g. as described by Zot, H. G. and Puett, D. in J. Biol.. . .
DETD . . . (see e.g. Milton Harris, J. (ed) "Poly(ethylene glycol) chemistry, biotechnical and biomedical applications" Plenum Press, New York, 1992). PEGs are **soluble** in most solvents, including

water, and are highly hydrated in aqueous environments, with two or three water molecules bound to. . . Furthermore, PEGs may readily be modified and bound to other molecules with only little effect on their chemistry. Their advantageous **solubility** and biological properties are apparent from the many possible uses of PEGs and copolymers thereof, including block copolymers such as. . .

DETD [0118] iv) polyvinyl alcohols, which are water-**soluble** and generally regarded as biocompatible (see e.g. Langer, R. in J. Control. Release (1991) 16, 53-60);

DETD . . . Arg at pH 7-8

ASIB (1)	--SH	photoreactive	iodinable
ASBA (1)	--COOH	photoreactive	iodinable
EDC	--NH.sub.2	--COOH	zero-length linker
GMBS	--NH.sub.2	--SH	
sulfo-GMBS	--NH.sub.2	--SH	water-**soluble**
HSAB	--NH.sub.2	photoreactive	
sulfo-HSAB	--NH.sub.2	photoreactive	water-**soluble**
MBS	--NH.sub.2	--SH	
sulfo-MBS	--NH.sub.2	--SH	water-**soluble**
M.sub.2C.sub.2H	carbohydrate	--SH	
MPBH	carbohydrate	--SH	
NHS-ASA (1)	--NH.sub.2	photoreactive	iodinable
sulfo-NHS-ASA (1)	--NH.sub.2	photoreactive	water-**soluble**, iodinable
sulfo-NHS-LC-ASA (1)	--NH.sub.2	photoreactive	water-**soluble**, iodinable
PDPH	carbohydrate	--SH	disulphide linker
PNP-DTP	--NH.sub.2	photoreactive	
SADP	--NH.sub.2	photoreactive	disulphide linker
sulfo-SADP	--NH.sub.2	photoreactive	water-**soluble** disulphide linker
SAED	--NH.sub.2	photoreactive	disulphide linker
SAND	--NH.sub.2	photoreactive	water-**soluble** disulphide linker
SANPAH	--NH.sub.2	photoreactive	
sulfo-SANPAH	--NH.sub.2	photoreactive	water-**soluble**
SASD (1)	--NH.sub.2	photoreactive	water-**soluble** iodinable disulphide linker
SIAB	--NH.sub.2	--SH	
sulfo-SIAB	--NH.sub.2	--SH	water-**soluble**
SMCC	--NH.sub.2	--SH	
sulfo-SMCC	--NH.sub.2	--SH	water-**soluble**
SMPB	--NH.sub.2	--SH	
sulfo-SMPB	--NH.sub.2	--SH	water-**soluble**
SMPT	--NH.sub.2	--SH	
sulfo-LC-SMPT	--NH.sub.2	--SH	water-**soluble**
SPDP	--NH.sub.2	--SH	
sulfo-SPDP	--NH.sub.2	--SH	water-**soluble**
sulfo-LC-SPDP	--NH.sub.2	--SH	water-**soluble**
sulfo-SAMCA (2)	--NH.sub.2	photoreactive	
sulfo-SAPB	--NH.sub.2	photoreactive	water-**soluble**

Notes:
(1) = iodinable;
(2) = fluorescent

Linking agent	Reactivity	Comments
Homobifunctional linking agents		
BS	--NH.sub.2	
BMH	--SH	
BASED (1)	photoreactive	iodinable disuiphide linker
BSCOES	--NH.sub.2	
sulfo-BSCOES	--NH.sub.2	water-**soluble**
DFDNB	--NH.sub.2	
DMA	--NH.sub.2	
DMP	--NH.sub.2	
DMS	--NH.sub.2	
DPDPB	--SH	disulphide linker
DSG	--NH.sub.2	
DSP	--NH.sub.2	disulphide linker
DSS	--NH.sub.2	
DST	--NH.sub.2	
sulfo-DST	--NH.sub.2	water-**soluble**
DTBP	--NH.sub.2	disulphide linker
DTSSP	--NH.sub.2	disulphide linker
EGS	--NH.sub.2	
sulfo-EGS	--NH.sub.2	water- **soluble**
SPBP	--NH.sub.2	
Biotinylation agents		
biotin-BMCC	--SH	
biotin-DPPE*		preparation of biotinylated liposomes
biotin-LC-DPPE*		preparation of biotinylated liposomes
biotin-HPDP	--SH	disuiphide linker
biotin-hydrazide	carbohydrate	
biotin-LC-hydrazide	carbohydrate	
iodoacetyl-LC-biotin	--NH.sub.2	
NHS-iminobiotin	--NH.sub.2	reduced affinity for avidin
NHS-SS-biotin	--NH.sub.2	disuiphide linker
photoactivatable biotin	nucleic acids	
sulfo-NHS-biotin	--NH.sub.2	water-**soluble**
sulfo-NHS-LC-biotin	--NH.sub.2	

Notes:
DPPE = dipalmitoylphosphatidylethanolamine;
LC = long chain

Agents for protein modification		
Ellman's reagent	--SH	quantifies/detects/protects
DTT	--S.S--	reduction
2-mercaptoethanol	--S.S--	reduction
2-mercaptylamine	--S.S--. . .	

DETD . . . ciclotropium bromide, cicloxilic acid, cicloxolone, cicortonide, cicrotic acid, cidoxepin, cifenline, cifostodine, ciglitazone, ciheptolane, ciladopa, cilastatine, cilazapril, cilazaprilat, cilobamine, cilofungin, cilostamide, **cilostazol**, ciltoprazine, cimaterol, cimemoxin, cimepanol, cimetidine, cimetropium bromide, cimoxatone, cinchonine, cinchophen, cinecromen, cinepaxadil, cinepazet, cinepazic acid, cinepazide, cinfenine, cinfenoac, cinflumide, cingestol,. . .

DETD . . . with an Evaporative Light Scattering Detector confirmed that the membranes of the microbubbles contained 4 mol % biotin-DPPE. The mean **particle diameter** of the microbubbles was 4 .mu.m measured by Coulter Counter. Ultrasound transmission measurements using a 3.5 MHz broadband transducer showed. . .

DETD [0190] Streptavidin is covalently bound to Succ-PEG.sub.3400-DSPE in the microbubble membranes by standard coupling methods using a water-**soluble** carbodiimide. The sample is placed on a roller table

during the reaction. After centrifugation the infranatant is exchanged with water. . .

DETD [0198] Streptavidin is covalently bound to Succ-PEG.sub.3400-DSPE in the microbubble membraness by standard coupling methods using a water-**soluble** carbodiimide. The sample is placed on a roller table during the reaction. After centrifugation the infranatant is exchanged with water. . .

DETD . . . Inactivated human thrombin was covalently bound to Succ-PEG.sub.3400-DSPE in the microbubbles from Example 16(b) by standard coupling methods using a water-**soluble** carbodiimide. The sample was placed on a roller table during the reaction. After centrifugation the infranatant was exchanged with water. . .

DETD . . . 0.25 mmol) in DMF (5 ml) was cooled to 0.degree. C. HOBt (39 mg, 0.25 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (water **soluble** carbodiimide) (48 mg, 0.25 mmol) were added. The reaction mixture was stirred at 0.degree. C. for 1 hour and then. . .

DETD . . . mg, 0.15 mmol) in DMF (5 ml) was added DIEA (26 ml, 0.15 mmol). HOBt (23 mg, 0.15 mmol) and water-**soluble** carbodiimide (WSC) (29 mg, 0.15 mmol) were added. The reaction mixture was stirred at room temperature overnight and then poured. . .

L7 ANSWER 8 OF 23 USPATFULL

AN 2002:22432 USPATFULL

TI Synergistic effect of a sulfonylurea and/or non-sulfonylurea Kchannel blocker, and a phosphodiesterase 3 type inhibitor

IN Fryburg, David A., East Lyme, CT, UNITED STATES
Parker, Janice C., Ledyard, CT, UNITED STATES

PI US 2002013268 A1 20020131

AI US 2001-829874 A1 20010410 (9)

PRAI US 2000-196728P 20000413 (60)

DT Utility

FS APPLICATION

LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340

CLMN Number of Claims: 25

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 1475

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods of treating non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance, the methods comprising the step of administering to a patient having or at risk of having non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose tolerance a synergistic amount of: 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also provides kits and pharmaceutical compositions that comprise: 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; and 2) a cAMP phosphodiesterase type 3 inhibitor. The present invention also relates to kits and pharmaceutical compositions that comprise 1) a sulfonylurea, a non-sulfonylurea K.sup.+ ATP channel blocker, or a sulfonylurea and a non-sulfonylurea K.sup.+ ATP channel blocker; 2) a cAMP phosphodiesterase type 3 inhibitor; and 3) an additional compound useful for the treatment of non-insulin dependent diabetes mellitus, insulin resistance, Syndrome X, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, polycystic ovary syndrome, cataracts, hyperglycemia, or impaired glucose

tolerance.

SUMM . . . the methods, kits, and pharmaceutical compositions, the cAMP phosphodiesterase type 3 inhibitor is milrinone, amrinone, enoximone, indolidan, cilostamide, lixazinone, imazodan, **cilostazol**, bemorandan, siguazodan, adibendan, pimobendan,saterinone, sulmazol, or vesnarinone.

DETD . . . can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required **particle size** in the case of dispersions, or by the use of surfactants.

DETD . . . compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, **solubilizing** agents and/or emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol,. . .

DETD . . . water supply. The combination of compounds can be directly metered into drinking water, preferably in the form of a liquid, water-**soluble** concentrate (such as an aqueous solution of a water **soluble** salt). Conveniently, the compounds of the present invention can also be added directly to the feed, as such, or in. . .

CLM What is claimed is:

. . . The method of claim 1 wherein the cAMP phosphodiesterase type 3 inhibitor is milrinone, amrinone, enoximone, indolidan, cilostamide, lixazinone, imazodan, **cilostazol**, bemorandan, siguazodan, adibendan, pimobendan,saterinone, sulmazol, or vesnarinone.

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 114-86-3, Phenformin 458-24-2, Fenfluramine 657-24-9, Metformin 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 2295-31-0D, Thiazolidinedione, derivs. 7440-62-2D, Vanadium, complexes 9004-10-8D, Insulin, analogs 10238-21-8, Glyburide 21187-98-4, Gliclazide 23602-78-0, Benfluorex 28299-33-4D, Imidazoline, derivs. 29094-61-9, Glipizide 37353-31-4, Vanadate 51037-30-0, Acipimox 56180-94-0, Acarbose 60719-84-8, Amrinone 66529-17-7, Midaglizole 68550-75-4, Cilostamide 72432-03-2, Miglitol 73384-60-8 **73963-72-1**, Cilostazol 74150-27-9, Pimobendan 74772-77-3, Ciglitazone 75358-37-1, Linogliride 77671-31-9, Enoximone 78415-72-2, Milrinone 79944-58-4, Idazoxan 80879-63-6, Emiglitate 81840-15-5, Vesnarinone 83480-29-9, Voglibose 84243-58-3, Imazodan 86615-96-5, BRL 35135 88431-47-4, Clomoxir 89197-32-0, Efaroxan 90505-66-1, Ro 16-8714 90730-96-4, BRL 37344 93479-97-1, Glimepiride 94192-59-3, Lixazinone 97322-87-7, Troglitazone 100510-33-6, Adibendan 100643-96-7, Indolidan 102669-89-6, Saterinone 104343-33-1, MDL-25637 105182-45-4, Fluparoxan 105816-04-4, Nateglinide 106612 94-6, Insulinotropin (human) 107444-51-9 109229-58-5, Englitazone 110605-64-6, Isaglidole 111025-46-8, Pioglitazone 112018-01-6, Bemoradan 115344-47-3, Siguazodan 122320-73-4, Rosiglitazone 122575-28-4, Naglivan 122830-14-2, Deriglidole 124083-20-1, Etomoxir 127214-23-7, Camiglibose 129689-30-1, ICI D7114 130714-47-5, WAG 994 133107-64-9 135062-02-1, Repaglinide 138908-40-4, CL316243 141200-24-0, Darglitazone 187887-46-3, Symlin 335149-21-8, AC2993
(sulfonylurea and/or non-sulfonylurea K+ ATP channel blocker and phosphodiesterase 3 type inhibitor synergism for treatment of non-insulin-dependent diabetes or other conditions)

L7 ANSWER 9 OF 23 USPATFULL

AN 2002:109187 USPATFULL

TI Polymorphic forms of 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone

IN Stowell, Grayson Walker, 710 Darwin Dr., Wilmington, NC, United States 28405
Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403

PI US 6388080 B1 20020514

AI US 2001-896448 20010629 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Morris, Patricia L.
LREP Myers Bigel Sibley & Sajovec, P.A., Fontana, Esq., Steven A.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 25 Drawing Figure(s); 25 Drawing Page(s)
LN.CNT 1171
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polymorphs Form B, Form C, and amorphous of 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone, commonly known as **cilostazol**, have been identified. These polymorphs may be formed in pure form, in combination with each other, in combination with other polymorphs of **cilostazol**, or together with other pharmaceutical agents. Processes for preparing these polymorphs, and combinations of these polymorphs, as well as methods of use and unit dosages of these polymorphic forms, and their combinations, are described.

AB Polymorphs Form B, Form C, and amorphous of 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone, commonly known as **cilostazol**, have been identified. These polymorphs may be formed in pure form, in combination with each other, in combination with other polymorphs of **cilostazol**, or together with other pharmaceutical agents. Processes for preparing these polymorphs, and combinations of these polymorphs, as well as methods. . .

SUMM . . . compositions and methods of preparing novel forms of the free base of 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone (hereinafter referred to by its generice name "**cilostazol**"). More particularly, novel crystalline forms of **cilostazol**, in the form of polymorphs B, C, and amorphous are disclosed. Most particularly, such forms of **cilostazol**, individually and in combinations thereof, with and without polymorphic Form A, are useful in pharmaceutical formulations and methods for using. . .

SUMM The compound 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone is generally known as the pharmaceutically active compound **cilostazol**. **Cilostazol** has been known to have a singular crystalline form (Form A), which is a free base and used as an. . .

SUMM **Cilostazol** has the following chemical structure: ##STR1##

SUMM **Cilostazol**, and several of its metabolites, are known inhibitors of phosphodiesterase and, more particularly, phosphodiesterase III. As a phosphodiesterase inhibitor (type III), **cilostazol** suppresses platelet aggregation and also acts as a direct arterial vasodilator. In addition to its reported vasodilator and antiplatelet effects, **cilostazol** has been proposed to have beneficial effects on plasma lipoproteins, increasing plasma high density lipoprotein cholesterol and apolipoprotein (See e.g.,. . . 98: 678-686 [1998]; Elam et al., Arterioscler Thromb. Vasc. Biol. 18: 1942-1947[1998]; Drug Evaluation Monographs, vol. 99, Micromedex Inc.). Additionally, **cilostazol** has been reported as useful for the treatment of sexual dysfunction in U.S. Pat. No. 6,187,790 to Cutler. **Cilostazol** free base is the API in the pharmaceutical drug product marketed under the trademark PLETAL.RTM. (Otsuka America Pharmaceutical, Inc., Rockville,. . .

SUMM Methods of preparation of **cilostazol** are set forth by Nishi et al. (Chem. Pharm. Bull. 31: 1151[1983], and U.S. Pat. No. 4,277,479, the disclosure of. . .

SUMM Use of **cilostazol** in pharmaceutical formulations has been limited by its low aqueous **solubility** and low bioavailability, which impede its efficient therapeutic use. Therefore, it would be beneficial if pharmaceutical chemists could provide a more **soluble** and, thus, more bioavailable drug product. These forms

could lead to lower doses of drug substance (per unit dose and. . .

SUMM . . . known as the final or finished dosage form), are well known in the pharmaceutical art to affect, for example, the **solubility**, stability, flowability, tractability, and compressibility of drug substances and the safety and efficacy of drug products (see, e.g., Knapman, K.. . .

SUMM . . . invention by X-ray powder diffraction and other methods of solid state characterization. Form A, the sole, previously known form of **cilostazol**, as prepared by the procedures described in the '479 patent, has been found to have low aqueous **solubility** and low-bioavailability. As such, Form A is not particularly well suited for commercial use in pharmaceutical formulations or for therapeutic. . .

SUMM A novel crystalline form of **cilostazol**, Form B, which possesses distinct advantages over the previously known Form A of **cilostazol** has now been prepared and characterized. In accordance with the present invention, a newly discovered polymorph, Form B of **cilostazol**, can be obtained in a pure form or in combination with other polymorphic forms of **cilostazol**. Form B is stable, and can be prepared free from contamination by solvates such as water or organic solvents such. . .

SUMM Another novel crystalline form of **cilostazol**, Form C, that has also been prepared and characterized, possesses distinct advantages over the previously known Form A of **cilostazol**, and is clearly distinguishable from other polymorphic forms of the present invention by X-ray powder diffraction and other methods of solid-state characterization. In accordance with the present invention, Form C of **cilostazol**, can be obtained in a pure form or in combination with other polymorphic forms of **cilostazol**. Form C is stable, and can be prepared free from contamination by solvates such as water or organic solvents such. . .

SUMM Another polymorphic form, amorphous **cilostazol**, has also been prepared and characterized. Such amorphous is clearly distinguishable from Form A and other polymorphic forms of **cilostazol** by X-ray powder diffraction and other solid-state methods of characterization. In accordance with the present invention, the newly discovered amorphous **cilostazol** can be obtained in a pure form or in combination with other polymorphic forms of **cilostazol**. Amorphous **cilostazol** can also be prepared free from other polymorphic forms of **cilostazol** and contamination by solvates such as water or organic solvents such as, for example, acetonitrile. As such, amorphous **cilostazol** may be used for commercial pharmaceutical formulations such as tablets and capsules, but is preferably used as an intermediate for the preparation of other polymorphic forms of **cilostazol**.

SUMM The present invention provides novel pure and combinations of polymorphic forms of **cilostazol**, each of which are useful for providing more desirable **solubility** and improved bioavailability characteristics, particularly when administered in pharmaceutical dosage forms.

DRWD FIG. 1 shows an ORTEP drawing of the single crystal structure of Form A **cilostazol**;

DRWD FIG. 2 shows an ORTEP drawing of the single crystal structure of Form C **cilostazol**;

DRWD FIG. 3 illustrates a Differential Scanning Calorimetry (DSC) thermogram for Form A **cilostazol**;

DRWD FIG. 4 illustrates a DSC thermogram for Form B **cilostazol**;

DRWD FIG. 5 illustrates a DSC thermogram for Form C **cilostazol**;

DRWD FIG. 6 illustrates a DSC thermogram for the combination of Forms A and B **cilostazol**;

DRWD FIG. 7 illustrates a DSC thermogram for the combination of Forms B and C **cilostazol**;

DRWD FIG. 8 illustrates a DSC thermogram for the combination of Forms A, B and C **cilostazol**;

DRWD FIG. 9 illustrates an X-ray powder diffraction (XRD) pattern for Form A

cilostazol;

DRWD FIG. 10 illustrates an XRD pattern for Form B **cilostazol**;

DRWD FIG. 11 illustrates an XRD pattern for Form C **cilostazol**;

DRWD FIG. 12 illustrates an XRD pattern comparing Form A **cilostazol**, Form B **cilostazol** and Form C **cilostazol**;

DRWD FIG. 13 illustrates an XRD pattern for amorphous **cilostazol**;

DRWD FIG. 14 illustrates an XRD pattern for the combination of Form A **cilostazol** (minor) and Form B **cilostazol** (major);

DRWD FIG. 15 illustrates a Fourier Transform Infrared Spectroscopy (FTIR) spectrum for Form A **cilostazol**;

DRWD FIG. 16 illustrates a FTIR spectrum for Form B **cilostazol**;

DRWD FIG. 17 illustrates a FTIR spectrum for Form C **cilostazol**;

DRWD FIG. 18 illustrates a FTIR spectrum overlaying Form A **cilostazol**, Form B **cilostazol** and Form C **cilostazol**;

DRWD FIG. 19 illustrates a FTIR spectrum for amorphous **cilostazol**; and,

DRWD FIG. 20 illustrates a Fourier Transform Raman Spectroscopy (FT-Raman) spectrum for Form A **cilostazol**;

DRWD FIG. 21 illustrates a FT-Raman spectrum for Form B **cilostazol**;

DRWD FIG. 22 illustrates a FT-Raman spectrum for Form C **cilostazol**;

DRWD FIG. 23 illustrates a FT-Raman spectrum for Form A **cilostazol**, Form B **cilostazol** and Form C **cilostazol**;

DRWD FIG. 24 illustrates a FT-Raman spectrum for amorphous **cilostazol**; and,

DRWD FIG. 25 illustrates a HPLC chromatographic overlay comparing various combinations of crystalline polymorphic forms of **cilostazol**.

DETD Preparation of Form A **cilostazol**, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone, is described in U.S. Pat. No. 4,277,479, the disclosure of such patent is herein incorporated by reference. The present invention is directed to polymorphic Form B of **cilostazol**, Form C of **cilostazol**, amorphous **cilostazol**, and combinations thereof, the preparation thereof, pharmaceutical formulations thereof, and the use of such polymorphs, preferably in pharmaceutical formulations, for. . . analysis for pure Form B as well as for samples containing Form B in combination with other polymorphic forms of **cilostazol**.

DETD As seen in FIGS. 1 and 2, as ORTEP drawings of the single crystal structures of Form A of **cilostazol** and Form C of **cilostazol**, respectively, show the different orientations of the two **cilostazol** molecules, thereby distinguishing these two forms of **cilostazol**. The ORTEP drawings are generated from the Oak Ridge Thermal Ellipsoid Program developed by Oak Ridge National Laboratory in Oak. . . single crystal structural analysis was not performed on Form B because of the microcrystalline nature of these samples, or amorphous **cilostazol** because of the non-crystalline nature thereof.

DETD X-ray single crystal unit cell parameters for Form A of **cilostazol** and Form C of **cilostazol** are compared in Table 1, below:

DETD Characterization of Form A of **cilostazol**, Form B of **cilostazol**, and Form C of **cilostazol** was further completed using DSC thermograms, shown in FIGS. 3, 4, and 5, respectively, with DSC thermograms for combinations of. . .

DETD The DSC thermogram in FIG. 6 shows several heat cycles of a **cilostazol** sample, with both Form A and Form B of **cilostazol** present in the third heat cycle. At the bottom of the thermogram, Form A of **cilostazol** appears during the first heating cycle at about 162.degree. C. Typically, the maximum temperature used for the first heating cycle. . . 200.degree. C. and, more typically about 200.degree. C. In this instance, after reaching a temperature of about 200.degree. C., the **cilostazol** was then cooled to about 0.degree. C., which is shown in the first cooling cycle of the DSC thermogram (immediately above the first heating cycle). Once the **cilostazol** sample reached approximately 0.degree. C., it

was immediately reheated to about 130.degree. C., shown in the second heating cycle of the DSC thermogram. During this reheating of the **cilostazol** sample, the sample appears to pass through a glass transition at about 35.degree. C. (onset at about 32.degree. C), with. . .

DETD . . . of about 200.degree. C. in the first heating cycle, the sample was then cooled to about 0.degree. C. Once the **cilostazol** sample reached about 0.degree. C., it was immediately reheated to about 100.degree. C, and held at this temperature for about 5 minutes. During this reheating, the **cilostazol** sample passed through the glass transition temperature at about 35.degree. C. (onset at about 32.degree. C.), but was not permitted. . .

DETD . . . C are not as great as Form A these data strongly suggest that Form B and Form C are more **soluble** than Form A of **cilostazol**.

DETD . . . in FIG. 12. As seen in FIG. 12, the XRD patterns of Form A, Form B and Form C of **cilostazol** demonstrate three distinct crystalline forms of the **cilostazol**, evidencing pure Form B and pure Form C. Characterization of amorphous **cilostazol** was also performed, as seen in the XRD pattern for amorphous **cilostazol** in FIG. 13. XRD was performed using a Siemens D500 Diffractometer (Madison, Wis.). Samples were analyzed from 2-40.degree. in 2.theta.. . .

DETD

TABLE 2

X-Ray Powder Diffraction
Significant Peaks of Form A of **Cilostazol**

2-Theta (degrees)	d(.ANG.)	Strength.sup.1	I %
5.2	16.89	vw	1.6
9.4	9.40	m	9.3
10.3	8.59	m	9.4

. . .

DETD

TABLE 3

X-Ray Powder Diffraction
Significant Peaks of Form B of **Cilostazol**

2-Theta (degrees)	d(.ANG.)	Strength.sup.1	I %
9.8	9.03	w	2.2
10.7	8.29	s	35.7
11.2	7.89	vw	1.9

. . .

DETD

TABLE 4

X-Ray Powder Diffraction
Significant Peaks of Form C of **Cilostazol**

2-Theta (degrees)	d(.ANG.)	Strength.sup.1	I %
5.0	17.51	w	0.8
8.6	10.22	s	10.1
9.7	9.12	vw	9.3

. . .

DETD The XRD pattern for the combination of a minor (approximately 10%) amount of Form A of **cilostazol** and a major (approximately 90%) amount of Form B of **cilostazol** is shown in FIG. 14.

DETD . . . and 17, respectively and an overlay of the three spectra are shown in FIG. 18. The FTIR spectrum for amorphous **cilostazol**

is shown in FIG. 19. FTIR was performed using a Nicolet Nexus 670 FTIR spectrometer with a Micro-FTIR attachment (Silicon. . .

DETD

TABLE 5

Major FTIR peaks of Form A, Form B, Form C and Amorphous **Cilostazol** (cm.sup.-1)

Form A of **cilostazol**	Form B of **cilostazol**	Form C of **cilostazol**	Amorphous **cilostazol**
3180	3181	3191	3210
3046	3054	3056	3063
2937	2940	2938	2934
2872	2868	2870	2861
1667	1662	1674. . .	

DETD The polymorphic forms of **cilostazol** are further characterized in FIGS. 20, 21, 22, and 24 for Form B, Form C, and amorphous **cilostazol** respectively. FT-Raman was performing using a Nicolet Nexus 670 FTIR spectrometer with a FT-Raman attachment. Samples were generally analyzed neat. . . of approximately 1 W. Major spectral bands of the FT-Raman for the Form A, Form B, Form C and amorphous **cilostazol** are listed in Table 6, below:

DETD

TABLE 6

Major FT-Raman peaks of Form A, Form B, Form C (cm.sup.-1) and Amorphous **Cilostazol**

Form A of **cilostazol**	Form B of **cilostazol**	Form C of **cilostazol**	Amorph ous **cilostazol**
3056	3054	3051	3059
2954	2941	2939	2940
2927	2914	2900	2905
2871	2868	2869	2861
1626	1616	1627. . .	

DETD . . . polymorphic combination to be as the same compound in solution (i.e., no degradation occurred in the thermal processing of the **cilostazol**) with a total amount of impurities of less than about 0.1% in each polymorphic combination.

DETD Accordingly, the amorphous, Form B, and Form C polymorphic forms of **cilostazol** have been characterized as distinct from Form A, and from each other. X-ray single crystal structural analysis, DSC, XRD, FTIR, and/or FT-Raman confirm the existence of the novel Form B of **cilostazol**, Form C, and amorphous **cilostazol**, and other various combinations of polymorphic forms of the present invention.

DETD In preparing amorphous **cilostazol**, any polymorphic form or combination of polymorphs of **cilostazol** (preferably Form A) is used as a starting material. The starting material is heated sufficiently for melting. Typically, when the heating rate is held constant at about 10.degree. C./minute Form A of **cilostazol** melts at a temperature at about 160.degree. C. Thus, temperatures from about 170.degree. C. or greater (preferably up to about 200.degree. C.) are used to ensure complete melt of the **cilostazol** starting material. Excessive temperatures that may alter the chemical characteristics, (e.g., cause degradation) of the **cilostazol** molecules are not used. As such, representative melting temperatures range from about 170.degree. C. to about 200.degree. C. Heating rates include any controllable heating process for complete melting of the **cilostazol** starting material. Representative static or variable

heating rates include, for example, from about 5.degree. C. per minute, 10.degree. C. per. . . atmosphere or, preferably, nitrogen purge, should be used to reduce or eliminate potential oxidative reactions during the melting of the **cilostazol**.

DETD The melted **cilostazol** is cooled from its molten state to about ambient temperature or below to provide amorphous **cilostazol**. The cooling steps described herein were all run at a cooling rate at about 10.degree. C./minute using the aforementioned Julabo FT900 intercooler chiller. The **cilostazol** sample should be maintained free of debris, such as dust and other foreign material and contaminates, and/or mechanical shock that would induce nucleation sites within the **cilostazol** sample. Rates of cooling are controlled to minimize thermal shock and performed in a manner to minimize contaminates and/or mechanical shock to the **cilostazol** which could induce nucleation sites which can induce crystallization. Typically, this will result in the formation Form A **cilostazol** . Representative cooling rates include, for example, from about 1.degree. C. per minute, 5.degree. C. per minute, 10.degree. C. per minute,. . .

DETD The identical steps of melting and cooling as described above are used for forming amorphous **cilostazol** are used for preparing Form B and/or Form C of **cilostazol**.

DETD . . . B and/or Form C, by reducing the temperature of the sample to about or below the glass transition temperature of **cilostazol** (about 32.degree. C.). Cooling such samples only to temperatures greater than about 32.degree. C. can provide such polymorph formation, primarily. . . this cooling step can significantly affect the purity of the polymorph(s) formed in subsequent steps, the temperature of the melted **cilostazol** is cooled to a temperature of about 0.degree. C. or less, and more preferably to temperatures of from about 0.degree.. . .

DETD . . . is the step that controls the formation of Form B, Form C, and various combinations of the polymorphic forms of **cilostazol**. Typically, three primary variables are responsible for such formation including: heating rate, maximum temperature (heating temperature), and holding time (collectively,. . . desired polymorph or combination of polymorphs, is formed. Accordingly, the teachings herein are intended to demonstrate the preparation of the **cilostazol** polymorphs of the present invention but, in no way, should be construed as limiting to the scope and breadth of. . .

DETD Heating rates are controlled in a manner to systematically impart energy into the **cilostazol** sample. Representative heating rates include from about 1.degree. C. per minute, 5.degree. C. per minute, 10.degree. C. per minute, 20.degree.. . .

DETD . . . herein. For example, when the cooled sample is heated to a temperature of 80.degree. C., the sample primarily remains amorphous **cilostazol**, generally, because the energy required to form crystalline polymorphic **cilostazol** is insufficient, particularly when the heating hold time is negligible. Similarly, holding the heating rate constant and a hold time. . . minutes, samples heated to about 90.degree. C. to about 105.degree. C. typically contain a combination of Form B and amorphous **cilostazol** at varying percentages of each. However, some Form C and, potentially, Form A, may be crystallized using these heating temperatures. . .

DETD . . . rate constant, with a heating temperature of about 100.degree. C., a hold time of about 5 minutes essentially eliminates amorphous **cilostazol**. Under these conditions the resulting product is predominately Form B, with the remaining portion being predominately Form C.

DETD After the heating step is completed and the desired polymorphic form(s) are obtained, the resulting **cilostazol** is recooled. With regard to Form B, the **cilostazol** is actively recooled or allowed to passively recool, preferably at a controlled rate (preferably about 10.degree. C./minute), to about ambient. . .

DETD Preferably, Form B is produced in a pure form (devoid of detectable amounts of other polymorphic forms of **cilostazol** as determined by FTIR, FT-Raman and/or X-Ray powder diffraction, as appropriate), or in substantially pure form having negligible other amounts of detectable polymorphic forms of **cilostazol**.

DETD During the final recooling step, the **cilostazol** is actively recooled or allowed to passively recool, preferably at a controlled rate, to about ambient temperature. preferably, Form C is produced in a pure form (devoid of detectable amounts of other polymorphic forms of **cilostazol** as determined by FTIR, FT-Raman, and/or X-ray powder diffraction, as appropriate), or in substantially pure form having negligible amounts of other detectable polymorphic forms of **cilostazol**.

DETD The present invention also provides pharmaceutical formulations comprising pure Form B, pure Form C, or pure amorphous **cilostazol**, either as the sole active ingredient or in combination with other active ingredients including, for example, other polymorphic forms of **cilostazol** or other pharmaceutically active agents, at least one pharmaceutically acceptable carrier, diluent, and/or excipient. Combinations of more than one polymorphic form of **cilostazol** are prepared via the described crystallization procedures or, for more precise combinations, via blending of pure or known polymorphic ratios. Preferred polymorphic combinations include, for example, Form B with Form C, Form A, and/or amorphous **cilostazol**; Form C with Form B, Form A, and/or amorphous **cilostazol**, and amorphous **cilostazol** with Form B, Form C and/or Form A of **cilostazol**.

DETD Preferably, the novel crystalline forms of **cilostazol**, Form B and Form C, and amorphous **cilostazol**, are in pure form. Pure form includes those samples of either Form B, Form C, or amorphous **cilostazol**, individually, that do not possess detectable amounts of any additional form of **cilostazol** as evidenced by XRD, FTIR, and/or FT-Raman analysis.

DETD . . . the term "active ingredient" refers to any of the embodiments set forth herein, particularly Form B, Form C, and amorphous **cilostazol**, individually and in combination among polymorphic forms of the present invention or other **cilostazol** polymorphic forms. More preferably polymorphic Form B and Form C of the present invention are used in pure form in. . .

DETD . . . being limited by the teachings as set forth herein, a solid dosage form, of Form B, Form C and/or amorphous **cilostazol**, of the present invention in combination with at least one pharmaceutically acceptable excipient, diluted by an excipient or enclosed within. . . or other container. Additionally, such pharmaceutical formulation may include a liquid formulation prepared from Form B, Form C and/or amorphous **cilostazol** API of the present invention in combination with at least one pharmaceutically acceptable excipient, diluted by an excipient or enclosed. . .

DETD . . . the following manner, although other techniques may be employed. The solid substances are gently ground or sieved to a desired **particle size**, and a binding agent is homogenized and suspended in a suitable solvent. The active ingredient(s) and auxiliary agents are mixed. . . of the mixture are then dried in controlled drying units for a pre-determined length of time to achieve a desired **particle size** and consistency. The granules of the dried mixture are gently sieved to remove any powder. To this mixture, disintegrating, anti-friction,. . .

DETD . . . about 25 mg to about 125 mg and more preferably from about 40 mg to about 110 mg of the **cilostazol** active ingredient(s). Other pharmaceutically active agents can also be added to the pharmaceutical formulations of the present invention at therapeutically. . . preferably about 25 mg to about 125 mg and more preferably about 40 mg to about 110 mg of such **cilostazol** active ingredient(s).

DETD . . . active ingredient(s) is for the reduction of intermittent

claudication in such subjects, typically manifested by an increased walking distance. The **cilostazol** active ingredients of the present invention may also be used for the treatment of other disease states related to vasodilation. . .

DETD The typical active daily dose of the **cilostazol** active ingredient(s) will depend on various factors such as, for example, the individual requirement of each patient, the route of. . .

DETD Preparation of Pure Form B of **Cilostazol**

DETD A sample of approximately 5 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 110.degree. C., and held at 110.degree. C. for five minutes. After holding the **cilostazol** at 110.degree. C. for five minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated in an undisturbed state by DSC at a rate of 10.degree. C. per minute to a final temperature about 170.degree. C., the sample showed an endothermic peak for Form B of **cilostazol** at approximately 138.degree. C. (onset observed at about 136.degree. C.) with a minor peak at 149.degree. C. which relates to. . .

DETD Preparation of Pure Form B of **Cilostazol**

DETD A sample of approximately 20 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 110.degree. C., and held at 110.degree. C. for five minutes. After holding the **cilostazol** at 110.degree. C. for five minutes, the **cilostazol** was cooled to 30.degree. C. at a rate of 10.degree. C. per minute. The sample was removed and analyzed by XRD, FTIR and FT-Raman which confirmed the sample as 100% Form B of **cilostazol**.

DETD Transformation of Pure Form B of **Cilostazol** to Form A of **Cilostazol**

DETD The resultant sample of Example 1A was disturbed with scratching, which caused the **cilostazol** sample to undergo a solid state phase transformation at approximately 119.degree. C. followed by an endotherm of melt at approximately. . .

DETD Preparation of Pure/Essentially Pure Form C of **cilostazol**

DETD A sample of approximately 14 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 0.degree. C., and held at 10.degree. C. for five minutes. After holding the **cilostazol** at 100.degree. C. for five minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated at a rate of 1 0.degree. C. per minute to a temperature of 45.degree. C. and held at 145.degree. C. for 5 minutes, after which time the **cilostazol** was then recooled to 0.degree. C. at a rate of 10.degree. C. per minute. Upon reheating in an undisturbed state,. . .

DETD Preparation of Pure Form C of **Cilostazol**

DETD A sample of approximately 22 mg of Form A **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace under a nitrogen purge of 40. . . 200.degree. C. (past the melting

point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 100.degree. C., and held at 100.degree. C. for five minutes. After holding the **cilostazol** at 100.degree. C. for five minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated at a rate of 0.degree. C. per minute to a temperature of 145.degree. C. and held for five minutes, after which time the **cilostazol** was then recooled to 30.degree. C. at a rate of 10.degree. C. per minute. A single crystal was obtained from. . . found to have a different polymorphic form than that of Form A or Form B (identified in Example 1). The **cilostazol** sample displayed a unique XRD powder pattern, FTIR and FT-Raman spectra and was identified as 100% Form C of **cilostazol**.

DETD Transformation from Form C to Form A of **Cilostazol**

DETD . . . at 10.degree. C. per minute. This disturbance of sample is believed to induce nucleation which preferentially causes Form A of **cilostazol** to form upon heating.

DETD Preparation of a Combination of Form B of **Cilostazol** and Form A of **Cilostazol** (about 60:40)

DETD A sample of approximately 7 mg of Form A **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 130.degree. C. The **cilostazol** was then cooled to 0.degree. C. at a rate of 10.degree. C. per minute.

DETD The **cilostazol** was then reheated in an undisturbed state by DSC from 0.degree. C. to 200.degree. C. at 10.degree. C. per minute.. . .

DETD Preparation of a combination of Form B of **cilostazol** and Form A of **cilostazol** (about 60:40)

DETD A sample of approximately 6 mg of Form A **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 0.degree. C. per minute. The molten **cilostazol** was cooled to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 120.degree. and held for five minutes. After holding for five minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute.

DETD The **cilostazol** was reheated in an undisturbed state by DSC from 0.degree. C. to 200.degree. C. at 0.degree. C. per minute. Two. . .

DETD Preparation of a Combination of Form A of **Cilostazol**, Form B of **Cilostazol** and Form C of **Cilostazol**

DETD A sample of approximately 5 mg of Form A **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 110.degree. C., and held at 110.degree. C. for 30 minutes. After holding the sample for 30 minutes at 110.degree. C., the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute.

DETD The **cilostazol** was reheated in an undisturbed state by DSC from 0.degree. C. to 200.degree. C. at 10.degree. C. per minute. Three. . .

DETD A sample of approximately 7 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 130.degree. C., and held at 130.degree. C. for five minutes. After holding the **cilostazol** at 130.degree. C. for the five minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated in an undisturbed state by DSC at a rate of 10.degree. C. per minute to a final temperature above 170.degree. C. The sample showed an endothermic peak for Form B of **cilostazol** at approximately 138.degree. C. (onset at about 135.degree. C.) with a minor peak at 149.degree. C. (onset at about 147.degree.. . .

DETD Preparation of pure Form B of **Cilostazol**

DETD A sample of approximately 8 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 120.degree. C. The **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated in an undisturbed state by DSC at a rate of 0.degree. C. per minute to a final temperature above 170.degree. C. The sample showed an endothermic peak for Form B of **cilostazol** at approximately 139.degree. C. (onset at about 136.degree. C.) with a minor peak at 147.degree. C. (onset at about 149.degree.. . .

DETD Preparation of Form B: Form C **Cilostazol** (about 66:34)

DETD A sample of approximately 8 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 110.degree. C. The **cilostazol** was then cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated in an undisturbed state by DSC at a rate of 10.degree. C. per minute to a final temperature above 170.degree. C. The sample showed an endothermic peak for Form B of **cilostazol** at approximately 138.degree. C. (onset at about 135.degree.) with a minor peak at 149.degree. C. (onset at about 147.degree. C.). . .

DETD Preparation of Form B: Form C **Cilostazol** (about 92:8)

DETD A sample of approximately 7 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 0.degree. C. per minute. The cooled **cilostazol** again was heated from 0.degree. C. to 130.degree. C., and held at 30.degree. C. for 30 minutes. After holding the **cilostazol** at 130.degree. C. for 30 minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 0.degree. C. per minute. The **cilostazol** was then reheated in an undisturbed state by DSC at a rate of 10.degree. C. per minute to a final temperature above 170.degree. C. The sample showed an endothermic peak for Form B of **cilostazol** at approximately 199.degree. C. (with a minor peak at 149.degree. C. which relates to

Form C. The peaks show a. . .

DETD Preparation of Form B: Form C **Cilostazol** (about 87:13)

DETD A sample of approximately 5 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 100.degree. C., and held at 100.degree. C. for five minutes. After holding the **cilostazol** for the five minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated in an undisturbed state by DSC at a rate of 10.degree. C. per minute to a final temperature above 170.degree. C. The sample showed an endothermic peak for Form B of **cilostazol** at approximately 138.degree. C. (onset at about 135.degree. C.) with a minor peak at 149.degree. C. (onset at about 147.degree.. . .

DETD Preparation of Form B: Form C **Cilostazol** (about 83:17)

DETD A sample of approximately 6 mg of Form A of **cilostazol** was placed in a vented, sealed aluminum holder and placed in a DSC furnace. Under a nitrogen purge of 40. . . 200.degree. C. (past the melting point of Form A) at a heating rate of 10.degree. C. per minute. The molten **cilostazol** was cooled within the furnace to approximately 0.degree. C. at a cooling rate of approximately 10.degree. C. per minute. The cooled **cilostazol** was reheated from 0.degree. C. to 120.degree. C., and held at 120.degree. C. for 30 minutes. After holding the **cilostazol** at 120.degree. C. for 30 minutes, the **cilostazol** was cooled to 0.degree. C. at a rate of 10.degree. C. per minute. The **cilostazol** was then reheated in an undisturbed state by DSC at a rate of 10.degree. C. per minute to a final temperature above 170.degree. C. The sample showed an endothermnic peak for Form B of **cilostazol** at approximately 139.degree. C. (onset at about 136.degree. C.) with a minor peak at 149.degree. C. (onset at about 147.degree.. . .

DETD A sample of Form A of **cilostazol** was placed on a glass slide and inserted into a hot stage microscope furnace. Hot stage microscopy provides an analytical technique that allows for heat manipulation of the **cilostazol** sample while visual observing changes utilizing a microscope apparatus. Samples of Form A **cilostazol** were heated to approximately 170.degree. C. and held until visually melted, then cooled by removing the glass slide and placing. . .

DETD At 70.degree. C.: a heating rate 1 degree per minute held for 5 minutes resulted in amorphous **cilostazol**; amorphous with about 5% Form B (HR=2, T=5); amorphous (HR=5, T=5); amorphous with about 5% Form B (HR=2, T=5); amorphous. . .

DETD Hot stage microscopy was performed to provide an indication of the trends of the solid state transformations of the **cilostazol**. If an alternative sample holder is used instead of glass (e.g., aluminum) the cooling process will need to be altered. . .

CLM What is claimed is:

1. A process for preparing Form C of **cilostazol**, comprising the steps of: melting a **cilostazol** starting material; cooling the melted **cilostazol**; and, heating the cooled **cilostazol** sufficient to induce a cold crystallization of Form C of **cilostazol**.

2. The process of claim 1, wherein the heating step is accomplished by: elevating the temperature of the cooled **cilostazol** to a temperature range from above the cold crystallization temperature to at less than about 130.degree. C.; and, holding said. . .

3. The process of claim 1, wherein the step of cooling the melted **cilostazol** comprises cooling to a temperature at or below about the glass transition temperature.

4. The process of claim 2, wherein the step of cooling the melted **cilostazol** comprises cooling to a temperature at or below about the glass transition temperature.

5. The process of claim 1, further comprising the step of: recooling the heated **cilostazol**.

6. A process for further purifying Form C of **cilostazol**, comprising the process of claim 5 and further comprising the step of reheating the recooled **cilostazol** to a temperature of from about 138.degree. C. to about 147.degree. C.

7. The process of claim 6, further comprising the step of: re-recooling the reheated **cilostazol**.

8. Form C of **cilostazol** prepared by the process of claim 1.

9. Form C of **cilostazol** prepared by the process of claim 2.

10. Form C of **cilostazol** prepared by the process of claim 3.

11. Form C of **cilostazol** prepared by the process of claim 4.

12. Form C of **cilostazol** prepared by the process of claim 5.

13. Form C of **cilostazol** prepared by the process of claim 6.

14. Form C of **cilostazol** prepared by the process of claim 7.

IT **73963-72-1**, Cilostazol
(polymorphic forms of cilostazol)

L7 ANSWER 10 OF 23 IFIPAT COPYRIGHT 2002 IFI DUPLICATE 5
AN 3579515 IFIPAT;IFIUDB;IFICDB
TI TRIGLYCERIDE-FREE COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF HYDROPHOBIC THERAPEUTIC AGENTS; PHARMACEUTICAL COMPOSITIONS CAPABLE OF **SOLUBILIZING** THERAPEUTICALLY EFFECTIVE AMOUNTS OF HYDROPHOBIC THERAPEUTIC AGENTS. CARRIER INCLUDES A HYDROPHILIC SURFACTANT AND A HYDROPHOBIC SURFACTANT, AQUEOUS DISPERSION
INF Chen; Feng-Jing, Salt Lake City, UT
Patel; Mahesh V., Salt Lake City, UT
IN Chen Feng-Jing; Patel Mahesh V
PAF Lipocine, Inc., Salt Lake City, UT
PA Lipocine Inc (57527)
EXNAM Page, Thurman K
EXNAM Channavajjala, Lakshmi
AG Reed, Dianne E.Reed & Associates
PI US 6294192 20010925
AI US 1999-258654 19990226
XPD 26 Feb 2019
FI US 6294192 20010925
DT UTILITY
FS CHEMICAL
FS GRANTED
MRN 009812 MFN: 0263
CLMN 74
GI 1 Drawing Sheet(s), 1 Figure(s).
AB The present invention relates to triglyceride-free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the

surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.

TI TRIGLYCERIDE-FREE COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF HYDROPHOBIC THERAPEUTIC AGENTS; PHARMACEUTICAL COMPOSITIONS CAPABLE OF **SOLUBILIZING** THERAPEUTICALLY EFFECTIVE AMOUNTS OF HYDROPHOBIC THERAPEUTIC AGENTS. CARRIER INCLUDES A HYDROPHILIC SURFACTANT AND A HYDROPHOBIC SURFACTANT, AQUEOUS DISPERSION

ECLM . . . oral administration of a therapeutic agent, containing a composition comprised of: (a) a hydrophobic therapeutic agent having an intrinsic water **solubility** of less than about 1 wt. % at 25 degree(s) C. and present in a therapeutically effective dosage for oral. . .

ACLM 31. The capsule of claim 1, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 50 nm.

32. The capsule of claim 31, wherein the clear aqueous dispersion has a **particle size** distribution having an average **particle size** of less than about 20 nm.

34. The capsule of claim 1, wherein the intrinsic water **solubility** is loss than about 0.1% by weight at 25 degree(s) C.

35. The capsule of claim 34, wherein the intrinsic water **solubility** is less than about0.01% by weight at 25 degree(s) C.

. . . ivermectin, amiodarone, zileuton, zafirlukast, albuterol, montelukast, azithromycin, ciprofloxacin, clarithromycin, dirithromycin, rifabutine, rifapentine, trovafloxacin, baclofen, ritanovir, saquinavir, nelfinavir, efavirenz, dicournarol, tirofibran, **cilostazol**, ticlidopine, clopidrogel, oprevelkin, paroxetine, sertraline, venlafaxine, bupropion, clomipramine, miglitol, repaglinide, glymepride, pioglitazone, rosigiltazone, troglitazone, glyburide, glipizide, glibenclamide, carbamezepine, fosphenytion, tiagabine,. . .

44. The capsule of claim 1, wherein the carrier further comprises a **solubilizer**.

45. The capsule of claim 44, wherein the **solubilizer** is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.

46. The capsule of claim 45, wherein the **solubilizer** is an alcohol or polyol selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol,. . .

47. The capsule of claim 45, wherein the **solubilizer** is an amide selected from the group consisting of 2-pyrrolidone, 2-piperidone, epsilon -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, polyvinylpyrrolidone, and. . .

48. The capsule of claim 45, wherein the **solubilizer** is an ester selected from the group consisting of ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate,. . .

49. The capsule of claim 44, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof,. . .

50. The capsule of claim 44, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol,. . .

51. The capsule of claim 44, wherein the **solubilizer** is triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycofuirol,. . .

52. The capsule of claim 44, wherein the **solubilizer** is triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol

or a mixture thereof.
53. The capsule of claim 44, wherein the **solubilizer** is present in the composition in an amount of about 400% or less by weight, based on the total weight. . .
54. The capsule of claim 53, wherein the **solubilizer** is present in the composition in an amount of about 200% or less by weight, based on the total weight. . .
55. The capsule of claim 54, wherein the **solubilizer** is present in the composition in an amount of about 100% or less by weight, based on the total weight. . .
56. The capsule of claim 55, wherein the **solubilizer** is present in the composition in an amount of about 50% or less by weight, based on the total weight. . .
57. The capsule of claim 56, wherein the **solubilizer** is present in the composition in an amount about 25% or less by weight, based on the total weight of. . .
. . . of claim 1, wherein the composition further comprises an additional amount of a hydrophobic therapeutic agent, said additional amount not **solubilized** in the carrier.
66. A capsule containing a pharmaceutical composition comprising: (a) a hydrophobic therapeutic agent having an intrinsic water **solubility** of less than about 1 percent by weight and present in a therapeutically effective dosage for oral administration, and (b). . . monoglycerides, acetylated diglyceridcs, propylene glycol mono fatty acid esters, propylene glycol di fatty acid esters, and mixtures thereof, and a **solubilizer** selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof and present in an. . .
67. The capsule of claim 66, wherein the **solubilizer** is an alcohol, a polyol, or a mixture thereof.
68. The capsule of claim 67, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols, glycerol, pentaerythritol, sorbitol,. . .
70. The capsule of claim 66, wherein the **solubilizer** is present in an amount of about 5% to 25% by weight relative to the combined weight of the hydrophilic. . .
. . . of a plurality of beads each coated with a composition comprising (a) a hydrophobic therapeutic agent having an intrinsic water **solubility** of less than about 1 wt. % at 25 degree(s) C., and present in a therapeutically effective amount for oral. . .
. . . comprised of a plurality of particles each comprising a composition of (a) a hydrophobic therapeutic agent having and intrinsic water **solubility** of less than about 1 wt. % at 25 degree(s) C. and present in a therapeutically effective amount for oral. . .

L7 ANSWER 11 OF 23 USPATFULL
AN 2001:188704 USPATFULL
TI Regulators of the hedgehog pathway, compositions and uses related thereto
IN Dudek, Henryk, Wellesley, MA, United States
Ji, Benxiu, Sharon, MA, United States
PI US 2001034337 A1 20011025
AI US 2001-867311 A1 20010529 (9)
RLI Continuation of Ser. No. US 1999-417564, filed on 14 Oct 1999, PENDING
PRAI US 1999-115642P 19990113 (60)
US 1999-119594P 19990210 (60)
US 1999-142124P 19990702 (60)
DT Utility
FS APPLICATION
LREP ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
CLMN Number of Claims: 38
ECL Exemplary Claim: 1
DRWN 19 Drawing Page(s)

LN.CNT 3831
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting a cell with a compound, such as a polypeptide or small molecule in an amount sufficient to control the aberrant growth state e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity. The present invention further makes available methods and reagents for ameliorating to consequences of hedgehog loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compound, such as a polypeptide or small molecule, in an amount sufficient to ameliorate the In certain embodiments, the subject compounds, e.g., a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in turn modulates activity of the hedgehog pathway.
DETD . . . Compounds which may inhibit a cAMP phosphodiesterase include amrinone, milrinone, xanthine, methylxanthine, anagrelide, cilostamide, medorinone, indolidan, rolipram, 3-isobutyl-1-methylxanthine (IBMX), chelerythrine, **cilostazol**, glucocorticoids, griseolic acid, etazolate, caffeine, indomethacin, papverine, MDL 12330A, SQ22536, GDPssS, clonidine, type III and type IV phosphodiesterase inhibitors, methylxanthines. . .
DETD [0378] Examples of pharmaceutically acceptable antioxidants include: (1) water **soluble** antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-**soluble** antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3). . .
DETD . . . liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, **solubilizing** agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene. . .
DETD . . . can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required **particle size** in the case of dispersions, and by the use of surfactants.
DETD . . . injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water **solubility**. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon. . .

L7 ANSWER 12 OF 23 USPATFULL
AN 2001:158338 USPATFULL
TI Regulators of the hedgehog pathway, compositions and uses related thereto
IN Dudek, Henryk, Wellesley, MA, United States
Ji, Benxiu, Sharon, MA, United States
PA Curis, Inc., Cambridge, MA, United States (U.S. corporation)
PI US 6291516 B1 20010918
AI US 1999-417564 19991014 (9)
PRAI US 1999-115642P 19990113 (60)
US 1999-119594P 19990210 (60)
US 1999-142124P 19990702 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Krass, Frederick
LREP Vincent, Matthew P., Halstead, David P.Ropes & Gray
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 19 Drawing Figure(s); 19 Drawing Page(s)
LN.CNT 3730

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting a cell with a compound, such as a polypeptide or small molecule in an amount sufficient to control the aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity. The present invention further makes available methods and reagents for ameliorating the consequences of hedgehog loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compound, such as a polypeptide or small molecule, in an amount sufficient to ameliorate the In certain embodiments, the subject compounds, e.g., a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in turn modulates activity of the hedgehog pathway.

DETD Compounds which may inhibit a cAMP phosphodiesterase include amrinone, milrinone, xanthine, methylxanthine, anagrelide, cilostamide, medorinone, indolidan, rolipram, 3-isobutyl-1-methylxanthine (IBMX), chelerythrine, **cilostazol**, glucocorticoids, griseolic acid, etazolate, caffeine, indomethacin, papverine, MDL 12330A, SQ 22536, GDPssS, clonidine, type III and type IV phosphodiesterase inhibitors,. . .

DETD Examples of pharmaceutically acceptable antioxidants include: (1) water **soluble** antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-**soluble** antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3). . .

DETD . . . liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, **solubilizing** agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene. . .

DETD . . . can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required **particle size** in the case of dispersions, and by the use of surfactants.

DETD . . . injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water **solubility**. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon. . .

L7 ANSWER 13 OF 23 USPATFULL

AN 2001:121093 USPATFULL

TI Clear oil-containing pharmaceutical compositions

IN Chen, Feng-Jing, Salt Lake City, UT, United States
Patel, Mahesh V., Salt Lake City, UT, United States

PA Lipocine Inc., Salt Lake City, UT, United States (U.S. corporation)

PI US 6267985 B1 20010731

AI US 1999-345615 19990630 (9)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Spear, James M.

LREP Reed, Dianne E.Reed & Associates

CLMN Number of Claims: 184

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3767

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to pharmaceutical compositions and methods for improved **solubilization** of triglycerides and improved delivery of therapeutic agents. Compositions of the present invention include a triglyceride and a carrier, where the carrier is formed from a

combination of at least two surfactants, at least one of which is hydrophilic. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the triglyceride and surfactants. An optional therapeutic agent can be incorporated into the composition, or can be co-administered with the composition. The invention also provides methods of enhancing triglyceride **solubility** and methods of treatment with therapeutic agents using these compositions.

AB The present invention relates to pharmaceutical compositions and methods for improved **solubilization** of triglycerides and improved delivery of therapeutic agents. Compositions of the present invention include a triglyceride and a carrier, where. . . be incorporated into the composition, or can be co-administered with the composition. The invention also provides methods of enhancing triglyceride **solubility** and methods of treatment with therapeutic agents using these compositions.

SUMM . . . present invention relates to drug and nutrient delivery systems, and in particular to pharmaceutical compositions and methods for the improved **solubilization** of triglycerides and improved delivery of therapeutic agents.

SUMM . . . drugs, nutritional agents, and cosmeceuticals, are conventionally formulated in oil/water emulsion systems. These conventional emulsions take advantage of the increased **solubility** of many therapeutic agents in oils (triglycerides). Thus, one conventional approach is to **solubilize** a therapeutic agent in a bioacceptable triglyceride solvent, such as a digestible vegetable oil, and disperse this oil phase in. . .

SUMM . . . suitable for delivering therapeutic agents through an aqueous environment is an oil-in-water emulsion. Such emulsions contain the hydrophobic therapeutic agent **solubilized** in an oil phase which is dispersed in an aqueous environment with the aid of a surfactant. The surfactant may. . . colloidal oil particles sizes are relatively large, ranging from several hundred nanometers to several microns in diameter, in a broad **particle size** distribution. Since the particle sizes are on the order of or greater than the wavelength range of visible light, such. . .

SUMM Although conventional triglyceride-based pharmaceutical compositions are useful in **solubilizing** and delivering some therapeutic agents, such compositions are subject to a number of significant limitations and disadvantages. Emulsions are thermodynamically. . . less optimal, less effective, and poorly-characterized state upon ultimate administration to a patient. Uncharacterized degradation is particularly disadvantageous, since increased **particle size** slows the rate of transport of the colloidal particle and digestion of the oil component, and hence the rate and. . . lead to poorly-characterized and potentially harmful changes in the effective dosage received by the patient. Moreover, changes in colloidal emulsion **particle size** are also believed to render absorption more sensitive to and dependent upon conditions in the gastrointestinal tract, such as pH,. . .

SUMM . . . water, stabilized by surfactants. Conventional microemulsions, however, present several safety and efficiency problems. The amount of triglyceride that can be **solubilized** in a conventional microemulsion is generally quite small, resulting in a poor loading capacity. In order to **solubilize** significant amounts of triglycerides, large amounts of hydrophilic surfactant and/or solvents must be used. These high concentrations of hydrophilic surfactant. . .

SUMM It is therefore an object of the present invention to provide pharmaceutical compositions capable of **solubilizing** greater amounts of triglycerides in a homogeneous aqueous dispersion.

SUMM It is another object of the present invention to provide pharmaceutical compositions capable of **solubilizing** therapeutically effective amounts of therapeutic agents, including pharmaceutical, nutritional, and cosmeceutical agents.

SUMM In accordance with these and other objects and features, the present

invention provides pharmaceutical compositions for improved **solubilization** of triglycerides, and improved delivery of therapeutic agents. It has been surprisingly found that pharmaceutical compositions containing significant amounts of. . .

SUMM . . . aqueous dispersion. In a particular aspect of this embodiment, the composition is capable of containing more triglyceride than can be **solubilized** in a clear aqueous dispersion having only one surfactant, the surfactant being hydrophilic.

SUMM . . . aqueous dispersion. In a particular aspect of this embodiment, the composition is capable of containing more triglyceride than can be **solubilized** in a clear aqueous dispersion having a hydrophilic surfactant but not having a hydrophobic surfactant.

SUMM In another embodiment, the present invention relates to methods of increasing the amount of triglyceride that can be **solubilized** in an aqueous system, by providing a composition including a triglyceride and a carrier, the carrier including at least two. . . solution so that a clear aqueous dispersion is formed. Within the clear aqueous dispersion, the triglyceride is capable of being **solubilized** in an amount greater than the amount of the triglyceride that remains **solubilized** in an aqueous dispersion of the triglyceride and a carrier having only one surfactant and having the same total surfactant. . .

SUMM In another embodiment, the present invention relates to methods of increasing the **solubilization** of a therapeutic agent in a composition, by providing the therapeutic agent in a composition of the present invention.

SUMM . . . forms a clear aqueous dispersion. The therapeutic agent is present in two amounts, a first amount of the therapeutic agent **solubilized** in the clear aqueous dispersion, and a second amount of the therapeutic agent that remains non-**solubilized** but dispersed.

SUMM . . . with an aqueous solution. Surprisingly, the present inventors have found that compositions including triglycerides and a combination of surfactants can **solubilize** therapeutically effective amounts of therapeutic agents in homogeneous, single-phase systems which are thermodynamically stable and optically clear. The optical clarity is indicative of a very small **particle size** within the aqueous dispersions, and this small **particle size** substantially reduces lipolysis dependence of the rate of bioabsorption, and other disadvantages of conventional triglyceride-containing formulations. Use of these formulations. . . rate and/or extent of absorption of the therapeutic agent. Advantageously, the compositions of the present invention are surprisingly able to **solubilize** greater amounts of triglycerides than conventional formulations, even when the total surfactant concentration is the same as in a conventional. . .

SUMM . . . amphiphilic compounds is the hydrophilic-lipophilic balance (the "HLB" value). Surfactants with lower HLB values are more hydrophobic, and have greater **solubility** in oils, whereas surfactants with higher HLB values are more hydrophilic, and have greater **solubility** in aqueous solutions.

SUMM Also included as oils in this category of surfactants are oil-**soluble** vitamins, such as vitamins A, D, E, K, etc. Thus, derivatives of these vitamins, such as tocopheryl PEG-1000 succinate (TPGS,. . .

SUMM . . . the pharmaceutical compositions and methods of the present invention are not particularly limited, as the compositions are surprisingly capable of **solubilizing** and delivering a wide variety of therapeutic agents. The therapeutic agents can be hydrophilic, lipophilic, amphiphilic or hydrophobic, and can be **solubilized** in the triglyceride; **solubilized** in the carrier; **solubilized** in both the triglyceride and the carrier; or present in the diluent. Optionally, the therapeutic agent can be present in a first, **solubilzed** amount, and a second, non-

solubilized (suspended) amount. Such therapeutic agents can be any agents having therapeutic or other value when administered to an animal, particularly. . .

SUMM In another embodiment, the therapeutic agent is hydrophobic. Hydrophobic therapeutic agents are compounds with little or no water **solubility**. Intrinsic water **solubilities** (i.e., water **solubility** of the unionized form) for hydrophobic therapeutic agents are less than about 1% by weight, and typically less than about. . .

SUMM . . . embodiment, the therapeutic agent is hydrophilic. Amphiphilic therapeutic agents are included within the class of hydrophilic therapeutic agents. Apparent water **solubilities** for hydrophilic therapeutic agents are greater than about 1% by weight, and typically greater than about 0.1% by weight. In. . .

SUMM . . . cephadrine, cephalexin, cerivistatin, cetrizine, chlopheniramine, chlophenisamine, chloproguanil, chlorambucil, chlordiazepoxide, chlormethiazole, chloroquine, chlorothiazide, chlorproguanil HCl, chlorpromazine, chlorpropamide, chlorprothiocene, chlorprothixene, chlorthalidone, cholecalciferol, **cilostazol**, cimetidine, cinnarizine, cinoxacin, ciprofloxacin, ciprofloxacin HCl, cisapride, citalopram, citrizine, clarithromycin, clemastine, clemastine fumarate, clemizole, clenbuterol, clinofibrate, clioquinol, clobazam, clofazimine, clofibrate,. . .

SUMM The amount of triglyceride that can be **solubilized** in a clear aqueous dispersion is increased by repeating the above procedure, but substituting a second hydrophilic surfactant, or a. . .

SUMM It has been surprisingly found that mixtures of surfactants including two hydrophilic surfactants can **solubilize** a greater relative amount of triglyceride than a single surfactant. Similarly, mixtures of surfactants including a hydrophilic surfactant and a hydrophobic surfactant can **solubilize** a greater relative amount of triglyceride than either surfactant by itself. It is particularly surprising that when the surfactant mixture includes a hydrophilic surfactant and a hydrophobic surfactant, the **solubility** of the triglyceride is greater than, for example, in the hydrophilic surfactant itself. Thus, contrary to conventional knowledge in the. . . art, the total amount of water-insoluble component (triglyceride plus hydrophobic surfactant) exceeds the amount of hydrophobic surfactant that can be **solubilized** by the same amount of hydrophilic surfactant. This unexpected finding shows a surprising and non-intuitive relationship between the hydrophilic and. . .

SUMM Other methods of characterizing optical clarity, such as direct **particle size** measurement and other methods known in the art may also be used.

SUMM If present, the therapeutic agent is **solubilized** in the triglyceride, the carrier, or in both the triglyceride and the carrier. Alternatively, the therapeutic agent can be **solubilized** in the aqueous medium used to dilute the preconcentrate to form an aqueous dispersion. The maximum amount of therapeutic agent that can be **solubilized** is readily determined by simple mixing, as the presence of any non-**solubilized** therapeutic agent is apparent upon visual examination.

SUMM In one embodiment, the therapeutic agent is present in an amount up to the maximum amount that can be **solubilized** in the composition. In another embodiment, the therapeutic agent is present in a first amount which is **solubilized**, and a second amount that remains unsolubilized but dispersed. This may be desirable when, for example, a larger dose of the therapeutic agent is desired. Although not all of the therapeutic agent is **solubilized**, such a composition presents advantages over conventional compositions, since at least a portion of the therapeutic agent is present in. . . dispersion phase. Of course, in this embodiment, the optical clarity of the resultant aqueous dispersion is determined before the second non-**solubilized** amount of the therapeutic agent is added.

SUMM . . . actually used in a pharmaceutical composition according to the present invention will be less than the maximum that can be **solubilized**, and it should be apparent that such compositions are also within the scope of the present invention.

SUMM 5. **Solubilizers**

SUMM If desired, the pharmaceutical compositions of the present invention can optionally include additional compounds to enhance the **solubility** of the therapeutic agent or the triglyceride in the composition. Examples of such compounds, referred to as "**solubilizers**", include:

SUMM and other **solubilizers** known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)), monooctanoin, diethylene glycol. . .

SUMM Mixtures of **solubilizers** are also within the scope of the invention. Except as indicated, these compounds are readily available from standard commercial sources.

SUMM Preferred **solubilizers** include triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred **solubilizers** include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

SUMM The amount of **solubilizer** that can be included in compositions of the present invention is not particularly limited. Of course, when such compositions are ultimately administered to a patient, the amount of a given **solubilizer** is limited to a bioacceptable amount, which is readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of **solubilizers** far in excess of bioacceptable amounts, for example, to maximize the concentration of therapeutic agent, with excess **solubilizer** removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the **solubilizer** can be in a concentration of 50%, 100%, 200%, or up to about 400% by weight, based on the amount of surfactant. If desired, very small amounts of **solubilizers** may also be used, such as 25%, 10%, 5%, 1% or even less. Typically, the **solubilizer** will be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by. . .

SUMM . . . are based on toxicity, specificity of the proteases and the potency of the inhibition. The inhibitor can be suspended or solubilized in the composition preconcentrate, or added to the aqueous diluent or as a beverage.

SUMM . . . solution, a buffer, an organic solvent, a beverage, a juice, or mixtures thereof. If desired, the diluent can include components **soluble** therein, such as a therapeutic agent, an enzyme inhibitor, **solubilizers**, additives, and the like.

SUMM . . . or proteins in a restricted area of drug liberation and absorption, and reduce or even exclude extensive dilution effects. Although **solubilizers** are typically used to enhance the **solubility** of a hydrophobic therapeutic agent, they may also render the compositions more suitable for encapsulation in hard or soft gelatin capsules. Thus, the use of a **solubilizer** such as those described above is particularly preferred in capsule dosage forms of the pharmaceutical compositions. If present, these **solubilizers** should be added in amounts sufficient to impart to the compositions the desired **solubility** enhancement or encapsulation properties.

SUMM . . . a clear aqueous dispersion. In a particular aspect of this embodiment, the composition can contain more triglyceride than can be **solubilized** in a clear aqueous dispersion having only one surfactant, the surfactant being hydrophilic. Thus, this embodiment provides a higher concentration. . .

SUMM . . . forms a clear aqueous dispersion. In a particular aspect of this embodiment, the composition contains more triglyceride than can be **solubilized** in a clear aqueous dispersion having a hydrophilic surfactant but not having a hydrophobic surfactant.

SUMM . . . forms a clear aqueous dispersion. The therapeutic agent is present in two amounts, a first amount of the therapeutic agent **solubilized** in the clear aqueous dispersion, and a second amount of the therapeutic agent that remains non-**solubilized** but dispersed.

SUMM . . . the appropriate amount of an alueous solution is added. Upon gentle mixing, a clear aqueous dispersion is formed. If any water-**soluble** enzyme inhibitors or additives are included, these may be added first as part of the pre-concentrate, or added later to. . .

SUMM . . . and a carrier, which forms a clear aqueous dispersion upon mixing with an aqueous solution, and an additional amount of non-**solubilized** therapeutic agent. Thus, the term "multi-phase" as used herein to describe these compositions of the present invention means a composition. . . particulate dispersion phase. The carrier and triglycerides are as described above, and can include any of the surfactants, therapeutic agents, **solubilizers** and additives previously described. An additional amount of therapeutic agent is included in the composition. This additional amount is not **solubilized** by the carrier, and upon mixing with an aqueous system is present as a separate dispersion phase. The additional amount. . . Thus, upon dilution, the composition contains two phases: a clear aqueous dispersion of the triglyceride and surfactants containing a first, **solubilized** amount of the therapeutic agent, and a second, non-**solubilized** amount of the therapeutic agent dispersed therein. It should be emphasized that the resultant multi-phase dispersion will not have the optical clarity of a dispersion in which the therapeutic agent is fully **solubilized**, but will appear to be cloudy, due to the presence of the non-**solubilized** phase. Such a formulation may be useful, for example, when the desired dosage of a therapeutic agent exceeds that which can be **solubilized** in the carrier and/or triglyceride. The formulation may also contain additives, as described above.

SUMM One skilled in the art will appreciate that a therapeutic agent may have a greater **solubility** in the pre-concentrate composition than in the aqueous dispersion, so that meta-stable, supersaturated solutions having apparent optical clarity but containing a therapeutic agent in an amount in excess of its **solubility** in the aqueous dispersion can be formed. Such super-saturated solutions, whether characterized as clear aqueous dispersions (as initially formed) or. . .

SUMM . . . of gentle heating, if desired. It is convenient to consider the therapeutic agent as divided into two portions, a first **solubilizable** portion which will be **solubilized** and contained within the clear aqueous dispersion upon dilution, and a second non-**solubilizable** portion which will remain non-**solubilized**. When the ultimate dosage form is non-aqucous, the first and second portions of the therapeutic agent are both included in. . . and upon dilution in an aqueous system, the composition will form the two phases as described above, with the second non-**solubilizable** portion of the therapeutic agent dispersed or suspended in the aqueous system, and the first **solubilizable** portion of the therapeutic agent **solubilized** in the composition. Alternatively, when the ultimate dosage form is aqueous, the pre-concentrate can be prepared including only the first, **solubilizable** portion of the therapeutic agent. This pre-concentrate can then be diluted in an aqueous system to form a clear aqueous dispersion, to which is then added the second, non-**solubilizable** portion of the therapeutic agent to form a multi-phase aqueous composition.

SUMM In another embodiment, the present invention relates to methods of increasing the **solubilization** of a therapeutic agent in a

composition, by providing the therapeutic agent in a composition of the present invention. The. . . is surprisingly found that by using the combinations of triglycerides and surfactants described herein, greater amounts of triglycerides can be **solubilized**, without resort to unacceptably high concentrations of hydrophilic surfactants.

SUMM . . . herein, it should be appreciated that the optical clarity of the aqueous phase will be obscured by the dispersed particulate non-**solubilized** therapeutic agent.

SUMM Robustness to dilution: the dispersions are surprisingly stable to dilution in aqueous solution. The hydrophobic therapeutic agent remains **solubilized** for at least the period of time relevant for absorption.

SUMM . . . disadvantage that bioabsorption of the therapeutic agents contained therein is dependent upon enzymatic degradation (lipolysis) of the triglyceride components. The **solubilization** of the triglyceride in an aqueous medium is usually limited if only a hydrophilic surfactant is used to disperse the. . . this case, the large size of the triglyceride particles impedes the transport and absorption of the triglyceride or therapeutic agent **solubilized** in the triglyceride or in the carrier. In addition, the large, thermodynamically unstable triglyceride particles could further impose a risk. . .

SUMM To achieve a high level of fully-**solubilized** triglyceride would require an amount of the hydrophilic surfactant exceeding that which would be bioacceptable. The pharmaceutical compositions of the. . . other problems of the prior art by adding a third component, a hydrophobic surfactant or a second hydrophilic surfactant. The **solubilization** of the triglyceride in the aqueous system is thereby unexpectedly enhanced. It is also unexpectedly found that the total amount of **solubilized** water-insoluble components, the triglyceride and hydrophobic surfactant, can greatly exceed the amount of the hydrophobic surfactant alone that can be **solubilized** using the same amount of the hydrophilic surfactant.

SUMM . . . hydrophilic surfactant. Further, the triglyceride-containing compositions of the present invention present small particle sizes, thus avoiding the problems of large **particle size** in conventional triglyceride-containing formulations and the concomitant safety concerns in parenteral administration.

SUMM . . . of the present invention are much smaller than the larger particles characteristic of vesicular, emulsion or microemulsion phases. This reduced **particle size** enables more efficient drug transport through the intestinal aqueous boundary layer, and through the absorptive brush border membrane. More efficient. . .

SUMM Less dependence on lipolysis: The lack of large **particle-size** triglyceride components provides pharmaceutical compositions less dependent upon lipolysis, and upon the many poorly characterized factors which affect the rate. . .

SUMM Non-dependence on bile and meal fat contents: Due to the higher **solubilization** potential over bile salt micelles, the present compositions are less dependent on endogenous bile and bile related patient disease states,. . .

SUMM Superior **solubilization**: The triglyceride and surfactant combinations used in compositions of the present invention enable superior loading capacity over conventional formulations. In. . . a specific therapeutic agent to more closely match the polarity distribution of the therapeutic agent, resulting in still further enhanced **solubilization**.

SUMM Faster dissolution and release: Due to the robustness of compositions of the present invention to dilution, the therapeutic agents remain **solubilized** and thus do not suffer problems of precipitation of the therapeutic agent in the time frame relevant for absorption. In. . . limited in dilution rate by entrapment in emulsion carriers. These factors avoid liabilities associated with the poor partitioning of lipid **solubilized** drug in to the aqueous phase, such as large emulsion

droplet surface area, and high interfacial transfer resistance, and enable. . .

SUMM . . . components that help to keep the therapeutic agent or absorption promoter, such as a permeation enhancer, an enzyme inhibitor, etc., **solubilized** for transport to the absorption site, but readily available for absorption, thus providing a more efficient transport and release.

SUMM Small size: Because of the small **particle size** in atqueous dispersion, the pharmaceutical compositions of the present invention allow for faster transport of the therapeutic agent through the. . .

DETD . . . composition is to include a therapeutic agent, the chosen therapeutic agent in a predetermined amount is added and stirred until **solubilized**. Optionally, **solubilizers** or additives are included by simple mixing.

DETD Triglyceride **Solubilization** in Conventional Formulations

DETD . . . does not substantially affect the clear, aqueous nature of composition. For the same reason, these compositions were free of additional **solubilizers** and other additives. The optical clarity was determined by visual inspection and/or by UV absorption (at 400 nm). When UV. . .

DETD TABLE 20

Binary Triglyceride-Surfactant **Solubility**

Hydrophilic Surfactant	PEG-35 Castor Oil (Incrocas	PEG-40H Castor Oil (Cremophor	PEG-6 Caprate/ Caprylate (Softigen	PEG-60 Corn Oil (Crovol. . .	PEG-45 Palm Kernel Oil

DETD TABLE 21A

Effects of Surfactant Combinations on the **Solubilization** of Triglycerides

	Composition in w/w ratio							
	1	2	3	4	5	6	7	8	9
Corn Oil	25	30	40	40. . .					

DETD TABLE 21A

Effects of Surfactant Combinations on the **Solubilization** of Triglycerides

	Composition in w/w ratio							
	1	2	3	4	5	6	7	8	9
Corn Oil	25	30	40	40. . .					

DETD . . . surfactant is replaced by a second hydrophilic surfactant in compositions 6-7, it is surprisingly found that the amount of triglyceride **solubilized** is similarly increased.

DETD . . . hydrophilic surfactant with a second hydrophilic surfactant or a hydrophobic surfactant dramatically increases the amount of triglyceride that can be **solubilized**.

DETD TABLE 22A

Solubilization of MCTs

	Composition in w/w ratio				
	19	20	21	22	23
Pureco 76	33	50	80	50	80
Cremophor RH-. . .					

DETD TABLE 22A

Solubilization of MCTs

	Composition in w/w ratio				
	19	20	21	22	23
Pureco 76	33	50	80	50	80
Cremophor RH-. . .					

DETD TABLE 22A

Solubilization of MCTs

	Composition in w/w ratio				
	19	20	21	22	23
Pureco 76	33	50	80	50	80

Cremophor RH-. . .

DETD Table 22 shows that the increased **solubilization** of the triglyceride is observed for MCTs as well as for LCTs, with a variety of surfactants. Table 22 additionally. . . shows that the same effect is observed in the presence of increased amounts of surfactants (compositions 23 and 27) and **solubilizers** (composition 23).

CLM What is claimed is:

. . . two surfactants, at least one of the surfactants being hydrophilic; and (c) a therapeutic agent which is capable of being **solubilized** in the triglyceride, the carrier, or both the triglyceride and the carrier, wherein the triglyceride and surfactants are present in. . .

. . . amounts such that the triglyceride can be present in an amount greater than the amount of the triglyceride that remains **solubilized** in an aqueous dispersion of the triglyceride and a carrier having only one surfactant, the surfactant being hydrophilic, and having. . .

. . . amounts such that the triglyceride can be present in an amount greater than the amount of the triglyceride that remains **solubilized** in an aqueous dispersion of the triglyceride and a carrier having only one surfactant, the surfactant being hydrophilic, and having. . .

. . . amounts such that the triglyceride can be present in an amount greater than the amount of the triglyceride that remains **solubilized** in an aqueous dispersion of the triglyceride and a carrier having a hydrophilic surfactant but not having a hydrophobic surfactant,. . .

48. The pharmaceutical composition of claim 1, which further comprises a **solubilizer**.

49. The pharmaceutical composition of claim 48, wherein the **solubilizer** is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.

53. The pharmaceutical composition of claim 48, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof,. . .

54. The pharmaceutical composition of claim 42, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol,. . .

55. The pharmaceutical composition of claim 48, wherein the **solubilizer** is selected from the group consisting of triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl. . .

56. The pharmaceutical composition of claim 48, wherein the **solubilizer** is selected from the group consisting of triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol and mixtures thereof.

59. The pharmaceutical composition of claim 58, wherein the enzyme inhibitor is **solubilized** or suspended in the preconcentrate.

. . . The pharmaceutical composition of claim 1, which further comprises an additional amount of the therapeutic agent, said additional amount not **solubilized** in the composition.

. . . least one hydrophilic surfactant and at least one hydrophobic surfactant; and (c) a therapeutic agent which is capable of being **solubilized** in the triglyceride, the carrier, or both the triglyceride and the carrier, wherein the triglyceride and surfactants are present in. . .

. . . amounts such that the triglyceride can be present in an amount greater than the amount of the triglyceride that remains **solubilized** in an aqueous dispersion of the triglyceride and a carrier having a hydrophilic surfactant but not having a hydrophobic surfactant,. . .
116. The pharmaceutical composition of claim 75, which further comprises a **solubilizer**.

117. The pharmaceutical composition of claim 116, wherein the **solubilizer** is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.

121. The pharmaceutical composition of claim 116, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof,. . .
122. The pharmaceutical composition of claim 116, wherein the **solubilizer** is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol,. . .
123. The pharmaceutical composition of claim 116, wherein the **solubilizer** is selected from the oroup consisting of triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl. . .
124. The pharmaceutical composition of claim 116, wherein the **solubilizer** is selected from the goup consisting of triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol and mixtures thereof.

127. The pharmaceutical composition of claim 126, wherein the enzyme inhibitor is **solubilized** or suspended in the preconcentrate.

. . . The pharmaceutical composition of claim 75, which further comprises an additional amount of the therapeutic agent, said additional amount not **solubilized** in the composition.

. . . of less than about 0.3 at 400 nm; (c) a first amount of a therapeutic agent, said first amount being **solubilized** in the triglyceride, the carrier, or both the triglyceride and the carrier; and (d) a second amount of a therapeutic agent, said second amount not **solubilized** in the triglyceride or the carrier.

. . . 400 nm, and wherein the triglyceride is present in an amount greater than the amount of the triglyceride that remains **solubilized** in an aqueous dispersion of the triglyceride and a carrier having only one surfactant, the surfactant being hydrophilic, and having. . .
162. The method of claim 151, wherein the therapeutic agent is provided by **solubilizing** the therapeutic agent in the triglyceride, in the carrier, or in both the triglyceride and the carrier.

167. A method of increasing the amount of a triglyceride that can be **solubilized** in a clear aqueous dispersion, the method comprising: (a) providing a composition comprising a triglyceride and a carrier, the carrier. . . 400 nm, and wherein the triglyceride is present in an amount greater than the amount of the triglyceride that remains **solubilized** in an aqueous dispersion of the triglyceride and a carrier having only one surfactant and having the same total surfactant. . .

L7 ANSWER 14 OF 23 USPATFULL
AN 2001:116526 USPATFULL
TI Targeted ultrasound contrast agents
IN Klaveness, Jo, Oslo, Norway

Rongved, P.ang.l, Oslo, Norway
L.o slashed.vhaug, Dagfinn, Oslo, Norway
PA Nycomed Imaging AS, Oslo, Norway (non-U.S. corporation)
PI US 6264917 B1 20010724
AI US 1997-958993 19971028 (8)
PRAI GB 1996-22366 19961028
GB 1996-22367 19961028
GB 1996-22368 19961028
GB 1997-699 19970115
GB 1997-8265 19970424
GB 1997-11842 19970606
GB 1997-11846 19970606
US 1997-49264P 19970607 (60)
US 1997-49268P 19970607 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Hartley, Michael G.
LREP Bacon & Thomas
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 5477
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, having reporters comprising gas-filled microbubbles stabilised by monolayers of film-forming surfactants, the reporter being coupled or linked to at least one vector.
DETD . . . or ionic bonds, or may be physically mixed into the stabilising material, particularly if the drug has similar polarity or **solubility** to the membrane material, so as to prevent it from leaking out of the product before it is intended to. . .
DETD . . . be employed; linking may be facilitated through addition of an amine or may result in direct vector-receptor coupling. Useful water **soluble** carbodiimides include 1-cyclohexyl-3-(2-morpholinyl-4-ethyl)carbodiimide (CMC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), e.g. as described by Zot, H. G. and Puett, D. in J. Biol.. .
.
DETD . . . (see e.g. Milton Harris, J. (ed) "Poly(ethylene glycol) chemistry, biotechnical and biomedical applications" Plenum Press, New York, 1992). PEGs are **soluble** in most solvents, including water, and are highly hydrated in aqueous environments, with two or three water molecules bound to. . . Furthermore, PEGs may readily be modified and bound to other molecules with only little effect on their chemistry. Their advantageous **solubility** and biological properties are apparent from the many possible uses of PEGs and copolymers thereof, including block copolymers such as. . .
DETD iv) polyvinyl alcohols, which are water-**soluble** and generally regarded as biocompatible (see e.g. Langer, R. in J. Control. Release (1991) 16, 53-60);
DETD . . . selectively

			with Arg at pH 7-8
ASIB(1)	-SH	photoreactive	iodinable
ASBA(1)	-COOH	photoreactive	iodinable
EDC	-NH.sub.2	-COOH	zero-length linker
GMBS	-NH.sub.2	-SH	
sulfo-GMBS	-NH.sub.2	-SH	water-**soluble**
HSAB	-NH.sub.2	photoreactive	
sulfo-HSAB	-NH.sub.2	photoreactive	water-**soluble**
MBS	-NH.sub.2	-SH	
sulfo-MBS	-NH.sub.2	-SH	water-**soluble**
M.sub.2 C.sub.2 H carbohydrate		-SH	
MPBH	carbohydrate	-SH	

NHS-ASA(1)	-NH.sub.2	photoreactive	iodinable
sulfo-NHS-ASA(1)	-NH.sub.2	photoreactive	water-**soluble**, iodinable
sulfo-NHS-LC-ASA(1)	-NH.sub.2	photoreactive	water-**soluble**, iodinable
PDPH	carbohydrate	-SH	disulphide linker
PNP-DTP	-NH.sub.2	photoreactive	
SADP	-NH.sub.2	photoreactive	disulphide linker
sulfo-SADP	-NH.sub.2	photoreactive	water-**soluble** disulphide linker
SAED	-NH.sub.2	photoreactive	disulphide linker
SAND	-NH.sub.2	photoreactive	water-**soluble** disulphide linker
SANPAH	-NH.sub.2	photoreactive	
sulfo-SANPAH	-NH.sub.2	photoreactive	water-**soluble**
SASD(1)	-NH.sub.2	photoreactive	water-**soluble** iodinable disulphide linker
SIAB	-NH.sub.2	-SH	
sulfo-SIAB	-NH.sub.2	-SH	water-**soluble**
SMCC	-NH.sub.2	-SH	
sulfo-SMCC	-NH.sub.2	-SH	water-**soluble**
SMPB	-NH.sub.2	-SH	
sulfo-SMPB	-NH.sub.2	-SH	water-**soluble**
SMPT	-NH.sub.2	-SH	
sulfo-LC-SMPT	-NH.sub.2	-SH	water-**soluble**
SPDP	-NH.sub.2	-SH	
sulfo-SPDP	-NH.sub.2	-SH	water-**soluble**
sulfo-LC-SPDP	-NH.sub.2	-SH	water-**soluble**
sulfo-SAMCA(2)	-NH.sub.2	photoreactive	
sulfo-SAPB	-NH.sub.2	photoreactive	water-**soluble**

Notes: (1) = iodinable; (2) = fluorescent

DETD	Linking agent	Reactivity	Comments
BS	-NH.sub.2		
BMH	-SH		
BASED(1)	photoreactive	iodinable disulphide linker	
BSCOES	-NH.sub.2		
sulfo-BSCOES	-NH.sub.2	water-**soluble**	
DFDNB	-NH.sub.2		
DMA	-NH.sub.2		
DMP	-NH.sub.2		
DMS	-NH.sub.2		
DPDPB	-SH	disulphide linker	
DSG	-NH.sub.2		
DSP	-NH.sub.2	disulphide linker	
DSS	-NH.sub.2		
DST	-NH.sub.2		
sulfo-DST	-NH.sub.2	water-**soluble**	
DTBP	-NH.sub.2	disulphide linker	
DTSSP	-NH.sub.2	disulphide linker	
EGS	-NH.sub.2		
sulfo-EGS	-NH.sub.2	water-**soluble**	
SPBP	-NH.sub.2		

DETD	. . . biotin-LC-hydrazide	carbohydrate
iodoacetyl-LC-biotin	-NH.sub.2	
NHS-iminobiotin	-NH.sub.2	reduced affinity for avidin
NHS-SS-biotin	-NH.sub.2	disulphide linker

photoactivatable biotin nucleic acids
sulfo-NHS-biotin -NH.sub.2 water-**soluble**
sulfo-NHS-LC-biotin -NH.sub.2
Notes: DPPE = dipalmitoylphosphatidylethanolamine; LC = long chain
DETD . . . ciclotropium bromide, cicloxilic acid, cicloxolone, cicortonide, cicrotic acid, cidoxepin, cifenline, cifostodine, ciglitazone, ciheptolane, ciladopa, cilastatine, cilazapril, cilazaprilat, cilobamine, cilofungin, cilostamide, **cilostazol**, ciltoprazine, cimaterol, cimemoxin, cimepanol, cimetidine, cimetropium bromide, cimoxatone, cinchonine, cinchophen, cinecromen, cinepaxadil, cinepazet, cinepazic acid, cinepazide, cinfenine, cinfenoac, cinflumide, cingestol,. . .
DETD . . . with an Evaporative Light Scattering Detector confirmed that the membranes of the microbubbles contained 4 mol % biotin-DPPE. The mean **particle diameter** of the microbubbles was 4 .mu.m measured by Coulter Counter. Ultrasound transmission measurements using a 3.5 MHz broadband transducer showed. . .
DETD Streptavidin is covalently bound to Succ-PEG.sub.3400 -DSPE in the microbubble membranes by standard coupling methods using a water-**soluble** carbodiimide. The sample is placed on a roller table during the reaction. After centrifugation the infranatant is exchanged with water. . .
DETD Streptavidin is covalently bound to Succ-PEG.sub.3400 -DSPE in the microbubble membraness by standard coupling methods using a water-**soluble** carbodiimide. The sample is placed on a roller table during the reaction. After centrifugation the infranatant is exchanged with water. . .
DETD . . . human thrombin was covalently bound to Succ-PEG.sub.3400 -DSPE in the microbubbles from Example 16(b) by standard coupling methods using a water-**soluble** carbodiimide. The sample was placed on a roller table during the reaction. After centrifugation the infranatant was exchanged with water. . .
DETD . . . 0.25 mmol) in DMF (5 ml) was cooled to 0.degree. C. HOBt (39 mg, 0.25 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (water **soluble** carbodiimide) (48 mg, 0.25 mmol) were added. The reaction mixture was stirred at 0.degree. C. for 1 hour and then. . .
DETD . . . mg, 0.15 mmol) in DMF (5 ml) was added DIEA (26 ml, 0.15 mmol). HOBt (23 mg, 0.15 mmol) and water-**soluble** carbodiimide (WSC) (29 mg, 0.15 mmol) were added. The reaction mixture was stirred at room temperature overnight and then poured. . .

L7 ANSWER 15 OF 23 USPATFULL
AN 2001:111808 USPATFULL
TI Diagnostic/therapeutic agents having microbubbles coupled to one or more vectors
IN Klaveness, Jo, Oslo, Norway
Rongved, P.ang.l, Oslo, Norway
H.o slashed.gset, Anders, Oslo, Norway
Tolleshaug, Helge, Oslo, Norway
N.ae butted.vestad, Anne, Oslo, Norway
Hellebust, Halldis, Oslo, Norway
Hoff, Lars, Oslo, Norway
Cuthbertson, Alan, Oslo, Norway
L.o slashed.vhaug, Dagfinn, Oslo, Norway
Solbakken, Magne, Oslo, Norway
PA Nycomed Imaging AS, Oslo, Norway (non-U.S. corporation)
PI US 6261537 B1 20010717
AI US 1997-960054 19971029 (8)
RLI Continuation-in-part of Ser. No. US 1997-958993, filed on 28 Oct 1997
PRAI GB 1996-22366 19961028
GB 1996-22367 19961028
GB 1996-22368 19961028

GB 1997-699 19970115
GB 1997-8265 19970424
GB 1997-11842 19970606
GB 1997-11846 19970606
US 1997-49264P 19970607 (60)
US 1997-49265P 19970607 (60)
US 1997-49268P 19970607 (60)

DT Utility
FS GRANTED
EXNAM Primary Examiner: Hartley, Michael G.
LREP Bacon & Thomas, Fichter, Richard E.
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 5614
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, having reporters comprising gas-filled microbubbles stabilised by monolayers of film-forming surfactants, the reporter being coupled or linked to at least one vector.

DRWD . . . or ionic bonds, or may be physically mixed into the stabilising material, particularly if the drug has similar polarity or **solubility** to the membrane material, so as to prevent it from leaking out of the product before it is intended to. . .

DRWD . . . be employed; linking may be facilitated through addition of an amine or may result in direct vector-receptor coupling. Useful water **soluble** carbodiimides include 1-cyclohexyl-3-(2-morpholinyl-4-ethyl)carbodiimide (CMC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), e.g. as described by Zot, H. G. and Puett, D. in J. Biol.. .

DRWD . . . (see e.g. Milton Harris, J. (ed) "Poly(ethylene glycol) chemistry, biotechnical and biomedical applications" Plenum Press, New York, 1992). PEGs are **soluble** in most solvents, including water, and are highly hydrated in aqueous environments, with two or three water molecules bound to. . . Furthermore, PEGs may readily be modified and bound to other molecules with only little effect on their chemistry. Their advantageous **solubility** and biological properties are apparent from the many possible uses of PEGs and copolymers thereof, including block copolymers such as. . .

DRWD iv) polyvinyl alcohols, which are water-**soluble** and generally regarded as biocompatible (see e.g. Langer, R. in J. Control. Release (1991) 16, 53-60);

DRWD . . . selectively

				with Arg at pH 7-8
ASIB(1)	--SH	photoreactive	iodinable	
ASBA(1)	--COOH	photoreactive	iodinable	
EDC	--NH.sub.2	--COOH	zero-length linker	
GMBS	--NH.sub.2	--SH		
sulfo-GMBS	--NH.sub.2	--SH	water-**soluble**	
HSAB	--NH.sub.2	photoreactive		
sulfo-HSAB	--NH.sub.2	photoreactive	water-**soluble**	
MBS	--NH.sub.2	--SH		
sulfo-MBS	--NH.sub.2	--SH	water-**soluble**	
M.sub.2 C.sub.2 H carbohydrate	--SH			
MPBH	carbohydrate	--SH		
NHS-ASA(1)	--NH.sub.2	photoreactive	iodinable	
sulfo-NHS-ASA(1)	--NH.sub.2	photoreactive	water-**soluble**, iodinable	
sulfo-NHS-LC-ASA(1)	--NH.sub.2	photoreactive	water-**soluble**, iodinable	
PDPH	carbohydrate	--SH	disulphide linker	

PNP-DTP	--NH.sub.2	photoreactive	
SADP	--NH.sub.2	photoreactive	disulphide linker
sulfo-SADP	--NH.sub.2	photoreactive	water-**soluble** disulphide linker
SAED	--NH.sub.2	photoreactive	disulphide linker
SAND	--NH.sub.2	photoreactive	water-**soluble** disulphide linker
SANPAH	--NH.sub.2	photoreactive	
sulfo-SANPAH	--NH.sub.2	photoreactive	water-**soluble**
SASD(1)	--NH.sub.2	photoreactive	water-**soluble** iodinable disulphide linker
SIAB	--NH.sub.2	--SH	
sulfo-SIAB	--NH.sub.2	--SH	water-**soluble**
SMCC	--NH.sub.2	--SH	
sulfo-SMCC	--NH.sub.2	--SH	water-**soluble**
SMPB	--NH.sub.2	--SH	
sulfo-SMPB	--NH.sub.2	--SH	water-**soluble**
SMPT	--NH.sub.2	--SH	
sulfo-LC-SMPT	--NH.sub.2	--SH	water-**soluble**
SPDP	--NH.sub.2	--SH	
sulfo-SPDP	--NH.sub.2	--SH	water-**soluble**
sulfo-LC-SPDP	--NH.sub.2	--SH	water-**soluble**
sulfo-SAMCA(2)	--NH.sub.2	photoreactive	
sulfo-SAPB	--NH.sub.2	photoreactive	water-**soluble**

Homobifunctional linking agents

Linking agent	Reactivity	Comments
BS	--NH.sub.2	
BMH	--SH	
BASED(1)	photoreactive iodinable disulphide linker	
BSCOES	--NH.sub.2	
sulfo-BSCOES	--NH.sub.2	water-**soluble**
DFDNB	--NH.sub.2	
DMA	--NH.sub.2	
DMP	--NH.sub.2	
DMS	--NH.sub.2	
DPDPB	--SH	disulphide linker
DSG	--NH.sub.2	
DSP	--NH.sub.2	disulphide linker
DSS	--NH.sub.2	
DST	--NH.sub.2	
sulfo-DST	--NH.sub.2	water-**soluble**
DTBP	--NH.sub.2	disulphide linker
DTSSP	--NH.sub.2	disulphide linker
EGS	--NH.sub.2	
sulfo-EGS	--NH.sub.2	water-**soluble**
SPBP	--NH.sub.2	

Biotinylation agents

Agent	Reactivity	Comments
biotin-BMCC	--SH	
biotin-DPPE*		preparation of biotinylated liposomes
biotin-LC-DPPE*		preparation of biotinylatea liposomes
biotin-HPDP	--SH	disulphide linker
biotin-hydrazide	carbohydrate	
biotin-LC-hydrazide	carbohydrate	
iodoacetyl-LC-	--NH.sub.2	

biotin
NHS-iminobiotin --NH.sub.2 reduced affinity for
avidin
NHS-SS-biotin --NH.sub.2 disulphide linker
photoactivatable nucleic
biotin acids
sulfo-NHS-biotin --NH.sub.2 water-**soluble**
sulfo-NHS-LC- --NH.sub.2
biotin
Agents for protein modification
Agent Reactivity Function
Ellman's reagent --SH quantifies/detects/protects
DTT --S.S-- reduction
2- --S.S-- reduction
mercaptoethanol
2-mercaptylamine --S.S-- reduction
Traut's reagent --NH.sub.2 introduces --SH
SATA --NH.sub.2. . .
DRWD . . . ciclotropium bromide, cicloxilic acid, cicloxolone, cicortonide, cicrotic acid, cidoxepin, cifenline, cifostodine, ciglitazone, ciheptolane, ciladopa, cilastatine, cilazapril, cilazaprilat, cilobamine, cilofungin, cilostamide, **cilostazol**, ciltoprazine, cimaterol, cimemoxin, cimepanol, cimetidine, cimetropium bromide, cimoxatone, cinchonine, cinchophen, cinecromen, cinepaxadil, cinepazet, cinepazic acid, cinepazide, cinfenine, cinfenoac, cinflumide, cingestol,. . .
DETD . . . with an Evaporative Light Scattering Detector confirmed that the membranes of the microbubbles contained 4 mol % biotin-DPPE. The mean **particle diameter** of the microbubbles was 4 .mu.m measured by Coulter Counter. Ultrasound transmission measurements using a 3.5 MHz broadband transducer showed. . .
DETD Streptavidin is covalently bound to Succ-PEG.sub.3400 -DSPE in the microbubble membranes by standard coupling methods using a water-**soluble** carbodiimide. The sample is placed on a roller table during the reaction. After centrifugation the infranatant is exchanged with water. . .
DETD Streptavidin is covalently bound to Succ-PEG.sub.3400 -DSPE in the microbubble membraness by standard coupling methods using a water-**soluble** carbodiimide. The sample is placed on a roller table during the reaction. After centrifugation the infranatant is exchanged with water. . .
DETD . . . human thrombin was covalently bound to Succ-PEG.sub.3400 -DSPE in the microbubbles from Example 16(b) by standard coupling methods using a water-**soluble** carbodiimide. The sample was placed on a roller table during the reaction. After centrifugation the infranatant was exchanged with water. . .
DETD . . . 0.25 mmol) in DMF (5 ml) was cooled to 0.degree. C. HOBt (39 mg, 0.25 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (water **soluble** carbodiimide) (48 mg, 0.25 mmol) were added. The reaction mixture was stirred at 0.degree. C. for 1 hour and then. . .
DETD . . . mg, 0.15 mmol) in DMF (5 ml) was added DIEA (26 ml, 0.15 mmol). HOBt (23 mg, 0.15 mmol) and water-**soluble** carbodiimide (WSC) (29 mg, 0.15 mmol) were added. The reaction mixture was stirred at room temperature overnight and then poured. . .

L7 ANSWER 16 OF 23 USPATFULL
AN 2001:93131 USPATFULL
TI Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
IN Patel, Mahesh V., Salt Lake City, UT, United States
Chen, Feng-Jing, Salt Lake City, UT, United States
PA Lipocine, Inc., Salt Lake City, UT, United States (U.S. corporation)
PI US 6248363 B1 20010619

AI US 1999-447690 19991123 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Spear, James M.
LREP Reed, Dianne E.Reed & Associates
CLMN Number of Claims: 57
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 3302
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides solid pharmaceutical compositions for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or separately administered. In one embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compositions of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutrionals, cosmeceuticals and diagnostic agents.

SUMM Hydrophobic active ingredients, such as progesterone, cyclosporine, itraconazole and glyburide present delivery challenges due to their poor aqueous **solubility** and slow dissolution rate. Several commercial products of these hydrophobic drugs are available, the various products using different methods to. . .

SUMM For hydrophilic active ingredients, the formulation challenges are different. Although these compounds are readily **soluble** in the aqueous gastrointestinal environment, they are poorly absorbed, due to poor membrane permeability and/or enzymatic degradation. Surfactants and lipophilic. . .

SUMM Solid carriers for pharmaceutical active ingredients offer potential advantages over micronized drugs, emulsions or **solubilized** formulations. Solid carriers, typically of size less than about 2 mm, can easily pass through the stomach, thus making the. . .

SUMM . . . is an object of the invention to provide solid pharmaceutical compositions having active ingredients in a rapid dissolvable and more **solubilized** state therein.

SUMM It is another object of the invention to provide solid pharmaceutical compositions having more sustained and complete **solubilization** upon administration to a patient.

DETD . . . delivering a wide variety of active ingredients. The active ingredient can be hydrophilic, lipophilic, amphiphilic or hydrophobic, and can be **solubilized**, dispersed, or partially **solubilized** and dispersed, in the encapsulation coat. Alternatively, the active ingredient can be provided separately from the solid pharmaceutical composition, such. . .

DETD In one embodiment, the active ingredient agent is hydrophobic. Hydrophobic active ingredients are compounds with little or no water **solubility**. Intrinsic water **solubilities** (i.e., water **solubility** of the unionized form) for hydrophobic active ingredients are less than about 1% by weight, and typically less than about. . .

DETD . . . benzonatate, betamethasone, bicalutanide, budesonide, bupropion, busulphan, butenafine, calcifediol, calciprotiene, calcitriol, camptothecan, candesartan, capsaicin, carbamezepine, carotenes, celecoxib, cerivistatin, cetrizine, chlorpheniramine, cholecalciferol, **cilostazol**, cimetidine, cinnarizine, ciprofloxacin, cisapride, clarithromycin, clemastine, clomiphene, clomipramine, clopidrogel, codeine, coenzyme Q10, cyclobenzaprine,

cyclosporine, danazol, dantrolene, dexchlopheniramine, diclofenac, dicoumarol, digoxin,. . .

DETD . . . embodiment, the active ingredient is hydrophilic. Amphiphilic compounds are also included within the class of hydrophilic active ingredients. Apparent water **solubilities** for hydrophilic active ingredients are greater than about 0.1% by weight, and typically greater than about 1% by weight. In. . .

DETD . . . a hydrophilic surfactant. Hydrophilic surfactants can be used to provide any of several advantageous characteristics to the compositions, including: increased **solubility** of the active ingredient in the solid carrier; improved dissolution of the active ingredient; improved **solubilization** of the active ingredient upon dissolution; enhanced absorption and/or bioavailability of the active ingredient, particularly a hydrophilic active ingredient; and. . .

DETD . . . amphiphilic compounds is the hydrophilic-lipophilic balance (the "HLB" value). Surfactants with lower HLB values are more lipophilic, and have greater **solubility** in oils, whereas surfactants with higher HLB values are more hydrophilic, and have greater **solubility** in aqueous solutions.

DETD 2.20 Derivatives of Fat-**Soluble** Vitamins

DETD Derivatives of oil-**soluble** vitamins, such as vitamins A, D, E, K, etc., are also useful surfactants for the compositions of the present invention.. . .

DETD . . . mixtures of polyols with fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; polyethoxylated fat-**soluble** vitamins or derivatives; and mixtures thereof.

DETD 5.1. **Solubilizers**

DETD The pharmaceutical compositions of the present invention can optionally include one or more **solubilizers**, i.e., additives to increase the **solubility** of the pharmaceutical active ingredient or other composition components in the solid carrier. Suitable **solubilizers** for use in the compositions of the present invention include:

DETD and other **solubilizers** known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)), monooctanoin, diethylene glycol. . .

DETD Mixtures of **solubilizers** are also within the scope of the invention. Except as indicated, these compounds are readily available from standard commercial sources.

DETD Preferred **solubilizers** include triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred **solubilizers** include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

DETD The amount of **solubilizer** that can be included in compositions of the present invention is not particularly limited. Of course, when such compositions are ultimately administered to a patient, the amount of a given **solubilizer** is limited to a bioacceptable amount, which is readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of **solubilizers** far in excess of bioacceptable amounts, for example, to maximize the concentration of active ingredient, with excess **solubilizer** removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation.

DETD . . . are based on toxicity, specificity of the proteases and the potency of the inhibition. The inhibitor can be suspended or **solubilized** in the composition preconcentrate, or added to the aqueous diluent or as a beverage.

DETD . . . sucrose), and chemical binders (polymeric cellulose derivatives, such as carboxy methyl cellulose, HPC and HPMC; sugar syrups; corn syrup; water **soluble** polysaccharides such as acacia, tragacanth, guar and alginates; gelatin; gelatin hydrolysate; agar; sucrose; dextrose; and non-cellulosic binders, such as PVP,. . .

DETD . . . to reduce odor, to minimize gastrointestinal irritation, etc. The isolating effect is proportional to the thickness of the coating. Water **soluble** cellulose ethers are preferred for this application. HPMC and ethyl cellulose in combination, or Eudragit E100, may be particularly suitable. . .

DETD . . . 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent **solubility** profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the. . .

DETD Acrylic polymers (preferred). The performance of acrylic polymers (primarily their **solubility** in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic. . . copolymers and ammonio methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as **solubilized** in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal. . .

DETD . . . surfactants, antifoaming agents, lubricants, stabilizers such as hydroxy propyl cellulose, acid/base may be added to the coatings besides plasticizers to **solubilize** or disperse the coating material, and to improve coating performance and the coated product.

DETD . . . pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily **soluble** or partially **soluble** at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract.

DETD . . . to ester groups is approximately 1:2. Eudragit S.RTM is insoluble at pH below 5.5, but unlike Eudragit L-30-D.RTM, is poorly **soluble** in gastrointestinal fluids having pH of 5.5-7.0, such as is present in the small intestine media. This copolymer is **soluble** at pH 7.0 and above, i.e., the pH generally found in the colon. Eudragit S.RTM can be used alone as. . . to provide delivery of beginning at the large intestine via a delayed release mechanism. In addition, Eudragit S.RTM, being poorly **soluble** in intestinal fluids below pH 7, can be used in combination with Eudragit L-30-D.RTM, **soluble** in intestinal fluids above pH 5.5, in order to effect a delayed release composition. The more Eudragit L-30 D.RTM used. . . and delivery begins Both Eudragit L-30-D-RTM and Eudragit S.RTM can be substituted with other pharmaceutically acceptable polymers with similar pH **solubility** characteristics.

DETD . . . an example of such a coating. It is a combination of a water insoluble cationic methacrylate copolymer with a water **soluble** cellulose ether. In powder form, it is readily dispensible into an easily sprayable suspension that dries to leave a smooth. . .

DETD . . . molten solution of the encapsulation coat composition free of a dispersing medium. The coating solution can also be prepared by **solubilizing** or suspending the composition of the encapsulation coat in an aqueous medium, an organic solvent, a supercritical fluid, or a. . .

DETD . . . a molten solution of the composition of the solid carrier or a dispersion of the composition of the solid carrier **solubilized** or suspended in an aqueous medium, an organic solvent, a supercritical fluid, or a mixture thereof. Such solution or dispersion. . .

DETD . . . aspects, such as matrix materials, viscosity, and processing factors, such as temperature, atomization and cooling rate affect the quality (morphology, **particle size** distribution, polymorphism and dissolution characteristics) of spray congealed pellets. The spray congealed particles may be used in tablet granulation form,. . .

DETD Nanoencapsulation involves **solubilizing** an aqueous solution of

an active ingredient and other components in a weakly polar vehicle. Micelles are formed with the. . .

DETD Solvent-based coating is when the components of the invention are **solubilized** and/or dispersed in a solvent. The solvent can be aqueous. When the solvent is aqueous-based, the components can be emulsified. . . numbers are preferred. Solvent mixtures with other organic solvents or water are often employed to get appropriate viscosity and component **solubilization**. Typical solvents include ethanol, methanol, isopropanol, acetone, dichloromethane, trichloromethane and ethyl acetate. Appropriate polymers can also be added as needed. Cellulosic derivatives and polymethacrylates are particularly suitable additives for organic solvent coating. Dissolution and **solubilization** of the components is facilitated by rigorous stirring or heating. Plasticizers may be also be added to stimulate dissolution. Colorants. . .

DETD . . . temperature, atomization, atomization fluid temperature, or droplet size, spray type, spray rate, rate of coating droplet solidification on particle surfaces, **particle size**, shape, etc. Inert materials such as sodium chloride, citric acid, potassium chloride can serve as substrates. One skilled in the. . .

DETD . . . in formulating coated bead compositions to provide a wetting function, to enable hydrophobic drugs to properly adhere to beads and/or water-**soluble** binders. For example, U.S. Pat. No. 4,717,569 to Harrison et al. discloses coated bead compositions of hydrophobic steroid compounds wetted by a hydrophilic surfactant and adhered to the beads by a water-**soluble** binder. The steroid compound is present as finely divided particles, held to the beads by the binder. The present inventors. . . amounts necessary or appropriate for a wetting function, enable a pharmaceutical active ingredient to be fully or at least partially **solubilized** in the encapsulation coating material itself, rather than merely physically bound in a binder matrix. In fact, while binders can optionally be used in the compositions of the present invention, the higher surfactant concentrations of the present invention, i.e., **solubilizing** amounts, obviate the need for binders and render them optional instead of necessary.

DETD The amount of hydrophilic surfactant used in this embodiment can be adjusted so as to at least partially **solubilize** the pharmaceutical active ingredient, with the optional lipophilic surfactants and triglycerides chosen to further increase the pharmaceutical active ingredient's **solubility**.

DETD . . . the composition to a patient, the high levels of surfactants and other components present in the composition facilitate the rapid **solubilization** of the pharmaceutical active ingredient. Thus, while the prior art composition of Harrison contains a drug in a form which requires further **solubilization** in vivo, such as by emulsification and micellization in the gastrointestinal tract, the active ingredient in compositions of the present invention is at least partially **solubilized** in the composition itself, and is further provided with surfactants and other components in the composition to facilitate rapid dispersion (emulsification/micellization) and sustained **solubilization** of the active ingredient upon administration.

DETD The optional lipophilic surfactant and triglycerides can be used as desired to further enhance **solubilization** of the active ingredient, or to promote dispersion (emulsification/micellization) in vivo, or to promote in vivo absorption at the absorption. . .

DETD . . . hydrophilic surfactant. In this embodiment, the lipophilic surfactant or triglyceride can be present in amounts to enable at least partial **solubilization** of an active ingredient in the encapsulation coat, in the composition, or separately administered.

DETD . . . to form solid carriers in the absence of a seed substrate. Preferably, the components are chosen to at least partially **solubilize** the active ingredient, as described above.

CLM What is claimed is:

. . . wherein the encapsulation coat comprises an admixture of a therapeutically effective amount of a hydrophilic pharmaceutical active ingredient, an effective **solubilizing** amount of at least one hydrophilic surfactant, and a lipophilic additive selected from the group consisting of lipophilic surfactants, triglycerides, and combinations thereof, wherein the effective **solubilizing** amount of the at least one hydrophilic surfactant is an amount effective to partially or fully **solubilize** the pharmaceutical active ingredient in the encapsulation coat.

. . . pharmaceutical composition in the form of a solid carrier comprising an admixture of a hydrophilic pharmaceutical active ingredient, an effective **solubilizing** amount of at least one hydrophilic surfactant, and a lipophilic additive selected from the group consisting of lipophilic surfactants, triglycerides, and combinations thereof, wherein the effective **solubilizing** amount of the at least one hydrophilic surfactant is an amount effective to partially or fully **solubilize** the pharmaceutical active ingredient in the solid carrier.

9. The pharmaceutical composition of claim 1, wherein the hydrophilic active ingredient has an apparent water **solubility** of at least about 1 mg/mL.

. . . 21. The pharmaceutical composition of claim 20, wherein the substrate is an additive selected from the group consisting of a **solubilizer**, an enzyme inhibitor, an anti-adherent, an anticoagulant, an antifoaming agent, an antioxidant, a binder, a bufferant, a chelating agent, a. . .
35. The pharmaceutical composition of claim 6, wherein the hydrophilic active ingredient has an apparent water **solubility** of at least about 1 mg/mL.

46. The pharmaceutical composition of claim 6, which further comprises a **solubilizer**, an enzyme inhibitor, an anti-adherent, an anticoagulant, an antifoaming agent, an antioxidant, a binder, a bufferant, a chelating agent, a. . .

IT 69655-05-6, Didanosine 69756-53-2, Halofantrine 70288-86-7, Ivermectin 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 71486-22-1, Vinorelbine 72432-03-2, Miglitol 72559-06-9, Rifabutine 73384-59-5, Ceftriaxone 73590-58-6, Omeprazole **73963-72-1**, Cilostazol 74011-58-8, Enoxacin 74103-06-3, Ketorolac 74356-00-6, Cefotetan disodium 74381-53-6, Leuprolide acetate 75330-75-5, Lovastatin 75706-12-6, Leflunomide 76420-72-9, Enalaprilat 76470-66-1, Loracarbef 76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine 78110-38-0, Aztreonam 79350-37-1, Cefixime 79517-01-4, Octreotide acetate 79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9, Simvastatin 81093-37-0, Pravastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 81161-17-3, Esmolol hydrochloride 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 82626-48-0, Zolpidem 82952-64-5, Trimetrexate glucuronate 83799-24-0, Fexofenadine 83869-56-1, Granulocyte-macrophage colony stimulating factor 83881-51-0, Cetirizine 83905-01-5, Azithromycin 84057-84-1, Lamotrigine 84371-65-3, Mifepristone 84449-90-1, Raloxifene 84625-61-6, Itraconazole 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril 87679-37-6, Trandolapril 88150-42-9, Amlodipine 88669-04-9, Trospectomycin 89778-26-7, Toremifene 89987-06-4, Tiludronate 90357-06-5, Bicalutamide 91161-71-6, Terbinafine 93390-81-9, Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 94749-08-3, Salmeterol xinafoate 95233-18-4, Atovaquone 97240-79-4, Topiramate 97322-87-7, Troglitazone 97682-44-5, Irinotecan 98079-51-7, Lomefloxacin 98319-26-7, Finasteride 100986-85-4, Levofloxacin 101828-21-1, Butenafine 103577-45-3, Lansoprazole

103628-46-2, Sumatriptan 104227-87-4, Famciclovir 104987-11-3, Tacrolimus 105462-24-6, Residronate 106133-20-4, Tamsulosin 106392-12-5, Oxirane, polymer with methyloxirane, block 106650-56-0, Sibutramine 106819-53-8, Doxacurium chloride 106861-44-3, Mivacurium chloride 107648-80-6, Cefepime hydrochloride 107753-78-6, Zafirlukast 107950-52-7, Gonadotropin-releasing hormone 109319-16-6, Factor VIII 110871-86-8, Sparfloxacin 111025-46-8, Pioglitazone 111406-87-2, Zileuton 112965-21-6, Calcipotriene 113427-24-0 113665-84-2, Clopidogrel 113852-37-2, Cidofovir 115103-54-3, Tiagabine 116094-23-6, Insulin aspart 117976-89-3, Rabeprazole 118072-93-8, Zoledronate 118292-40-3, Tazarotene 119914-60-2, Grepafloxacin 120014-06-4, Donepezil 121368-58-9, Olpadronate 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan 124832-26-4, Valaciclovir 127759-89-1, Lobucavir 127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1, Paricalcitol 133040-01-4, Eprosartan 133107-64-9, Insulin lispro 134523-00-5, Atorvastatin 134678-17-4, Lamivudine 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan 139110-80-8, Zanamivir 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 139639-23-9, Tissue type plasminogen activator 142128-59-4, Terzolin 143003-46-7, Alglucerase 143011-72-7, Granulocyte colony stimulating factor 143831-71-4 144034-80-0, Rizatriptan 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 145941-26-0, Oprelvekin 146961-76-4, Alatrofloxacin 147059-72-1, Trovafloxacin 148553-50-8, Pregabalin 151126-32-8, Pramlintide 153559-49-0, Targretin 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155213-67-5, Ritonavir 157810-81-6, Indinavir sulfate 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir 160337-95-1, Insulin glargine 162011-90-7, Rofecoxib 165101-51-9, Becaplermin 169148-63-4, Insulin detemir 169590-42-5, Celecoxib 171599-83-0, Sildenafil citrate 173146-27-5, Denileukin diftitox 191588-94-0, TNK-tPA
(solid carriers for improved delivery of active ingredients in pharmaceutical compns.)

L7 ANSWER 17 OF 23 USPATFULL
AN 2001:10521 USPATFULL
TI GPIb-lipid complex and uses thereof
IN Matsuda, Hiroshi, Osaka, Japan
Kamide, Kaeko, Hirakata, Japan
Amatsuji, Yasuo, Hirakata, Japan
Imagawa, Takashi, Fukuoka, Japan
Ikeda, Yasuo, Tokyo, Japan
Murata, Mitsuru, Niiza, Japan
PA Yoshitomi Pharmaceutical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6177059 B1 20010123
WO 9729128 19970814
AI US 1998-117746 19981203 (9)
WO 1997-JP284 19970206
19981203 PCT 371 date
19981203 PCT 102(e) date
PRAI JP 1996-21482 19960207
DT Utility
FS Granted
EXNAM Primary Examiner: Russel, Jeffrey E.
LREP Sughrue, Mion, Zinn, Macpeak & Seas, PLLC
CLMN Number of Claims: 27
ECL Exemplary Claim: 11
DRWN No Drawings
LN.CNT 660
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A complex comprising a lipid and a conjugate of GPIb and lipid having a functional group, and use thereof. The GPIb-lipid complex of the present

invention is extremely useful as a platelet substitute, a pharmaceutical agent for the prophylaxis and treatment of angiopathy, vascular damages and thrombosis, a diagnostic for vWF deficiency and the like, a biological or medical reagent, a reagent for screening platelet aggregation suppressant or antithrombosis, and the like. The GPIb-lipid complex of the present invention is also useful as a diagnostic for finding the location of vascular lesion or thrombus formation, or a therapeutic agent therefor, since it accumulates at vascular lesions.

SUMM . . . conjugate may be prepared in the presence of a surfactant. The surfactant is not particularly limited as long as it **solubilizes** the lipid having a functional group. The use of a nonionic surfactant is preferable so that the structure of GPIb. . .

SUMM GPIb, lipid [(II)1] and lipid [(II)2] having a functional group **solubilized** with surfactant are mixed in a suitable aqueous solvent to allow formation of a bond of GPIb and the lipid. . .

SUMM The obtained GPIb-lipid complex has a **particle size** of about 50-500 nm, preferably about 100-400 nm. The number of GPIb molecules per particle is 250-3000 and surface density. . .

SUMM The anti-platelet agent is exemplified by aspirin, ticlopidine, **cilostazol**, prostacyclin and the like.

DETD The prepared GPIb liposome had a PC concentration of 1.365 mg/ml, protein concentration of 0.978 mg/ml and average **particle size** of 328 nm.

L7 ANSWER 18 OF 23 USPATFULL

AN 2000:121099 USPATFULL

TI Sustained-release microcapsule of amorphous water-**soluble** pharmaceutical active agent

IN Takada, Shigeyuki, Kobe, Japan
Kurokawa, Tomofumi, Hyogo-ken, Japan
Iwasa, Susumu, Tsuzuki-gun, Japan

PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)

PI US 6117455 20000912

AI US 1995-535386 19950928 (8)

PRAI JP 1994-236846 19940930

DT Utility

FS Granted

EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Tran, Susan

LREP Fitzpatrick, Cella, Harper & Scinto

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 1149

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A sustained-release microcapsule contains an amorphous water-**soluble** pharmaceutical agent having a **particle size** of from 1 nm-10 .mu.m and a polymer. The microcapsule is produced by dispersing, in an aqueous phase, a dispersion of from 0.001-90% (w/w) of an amorphous water-**soluble** pharmaceutical agent in a solution of a polymer having a wt. avg. molecular weight of 2,000-800,000 in an organic solvent to prepare an s/o/w emulsion and subjecting the emulsion to in-water drying.

TI Sustained-release microcapsule of amorphous water-**soluble** pharmaceutical active agent

AB A sustained-release microcapsule contains an amorphous water-**soluble** pharmaceutical agent having a **particle size** of from 1 nm-10 .mu.m and a polymer. The microcapsule is produced by dispersing, in an aqueous phase, a dispersion of from 0.001-90% (w/w) of an amorphous water-**soluble** pharmaceutical agent in a solution of a polymer having a wt. avg. molecular weight of 2,000-800,000 in an organic solvent. . .

SUMM The present invention relates to a microcapsule containing an amorphous water-**soluble** physiologically active substance. The present invention also relates to a process for producing it.

SUMM JP-A 57-118512 discloses a process for producing sustained-release microcapsules of a water-**soluble** drug which comprises encapsulating the drug by coacervation phase separation. This process has the following disadvantages: (1) the water-**soluble** drug is leaked out to the outer aqueous phase, and the drug entrapment ratio decreases, and it is difficult to. . .

SUMM The main object of the present invention is to provide a sustained-release microcapsule that has a high entrapment of a water-**soluble** drug and causes a small initial release.

SUMM . . . intensively studied to achieve the above objectives. As a result, it has been found that a microcapsule comprising an amorphous water-**soluble** physiologically active substance and a polymer has a high entrapment of the physiologically active substance and causes a small initial. . .

SUMM The present invention provides a microcapsule comprising an amorphous water-**soluble** physiologically active substance and a polymer.

SUMM . . . present invention also provides a microcapsule which is obtainable by dispersing in an aqueous phase a dispersion of an amorphous water-**soluble** physiologically active substance in a solution of a polymer in an organic solvent to prepare an s/o/w type emulsion and. . .

SUMM . . . also provides a process for producing a microcapsule, which comprises dispersing in an aqueous phase a dispersion of an amorphous water-**soluble** physiologically active substance in a solution of a polymer in an organic solvent to prepare an s/o/w type emulsion and. . .

DETD The present invention makes it possible to prepare a sustained-release microcapsule that contains a high content of a water-**soluble** physiologically active substance and causes a small initial release of the physiologically active substance.

DETD The amorphous physiologically active substance used in the present invention is **soluble** in water. The term "**soluble** in water" or "water-**soluble**" means that the water-**solubility** of the physiologically active substance is generally not less than about 1 g, preferably not less than about 3 g,. . . less than about 5 g, per 100 ml of water at 20.degree. C. Preferably, the physiologically active substance is readily **soluble** in water. The term "readily **soluble** in water" means that the water-**solubility** of the physiologically active substance is not less than about 5 g, preferably not less than about 10 g, per. . .

DETD The physiologically active substance is not specifically limited so long as it is amorphous and water-**soluble**. Preferably, the physiologically active substance is an acidic or neutral substance.

DETD wherein R.sup.1" is Ser or Aib, R.sup.2" is Met or a fat-**soluble** natural amino acid (e.g., Leu, Val, Trp), R.sup.3" is Leu, Ser, Lys or an aromatic amino acid (e.g., Tyr, Trp,. . . Phe), R.sup.4" is Gly or a D-amino acid (e.g., D-Gly, D-Ala), R.sup.5" Lys or Leu, R.sup.6" is Met or a fat-**soluble** natural amino acid (e.g., Leu, Val, Trp), R.sup.7" is Glu or a basic amino acid (e.g., Lys, Arg), R.sup.8" is. . .

DETD Examples of the anti-platelet aggregation agents include ticlopidine, **cilostazol**, alprostadil, limaprost, dipyridamole, ethyl icosapentaenoate, beraprost, ozagrel, aspirin, etc.

DETD The amount of the water-**soluble** physiologically active substance to be used varies with factors related to the particular kind of physiologically active substance, desired pharmacological. . .

DETD The physiologically active substance is preferably used in the form of microparticles. The average **particle size** of the physiologically active substance is generally about 1 nm to about 10 .mu.m, preferably about 1 nm to about. . .

DETD The polymer to be used in the present invention is a slightly water-**soluble** or water-insoluble polymer having biocompatibility. Examples of the polymers include biodegradable polymers such as poly fatty acid esters (e.g., polylactic. . .

DETD . . . acid/glycolic acid copolymer (PLGA), for example, the biodegradability (i.e., degradability in living bodies) is defined as the percentage (w/w) of water-**soluble** low-molecular weight fragments degraded from PLGA based on PLGA and it should be more than 10% in one year after. . .

DETD Examples of the osmotic pressure adjustors include water-**soluble** polyhydric alcohols; water-**soluble** monohydric alcohols; water-**soluble** inorganic materials (e.g., inorganic salts); water-**soluble** monosaccharides, disaccharides, oligosaccharides and polysaccharides or their derivatives; water-**soluble** organic acids or salts thereof; water-**soluble** amino acids; water-**soluble** peptides, proteins or their derivatives; etc. Preferred examples thereof are water-**soluble** polyhydric alcohols; water-**soluble** inorganic acids; water-**soluble** monosaccharides, disaccharides, oligosaccharides and polysaccharides or their derivatives; and water-**soluble** organic acids and their salts. In particular, salts, water-**soluble** polyhydric alcohols and water-**soluble** inorganic acids are preferred.

DETD Examples of the above water-**soluble** inorganic salts include alkaline metal halides such as potassium chloride, sodium chloride, potassium bromide, sodium bromide, potassium iodide, sodium iodide,. . .

DETD Examples of the above water-**soluble** polyhydric alcohols include dihydric alcohols (e.g., glycerin, etc.), pentahydric alcohols (e.g., arabitol, xylitol, adonitol, etc.), hexahydric alcohols (e.g., mannitol, sorbitol,. . .

DETD Examples of the water-**soluble** monohydric alcohols include methanol, ethanol, isopropyl alcohol, etc. In particular, ethanol is preferred.

DETD Examples of the above water-**soluble** monosaccharides include pentoses (e.g., arabinose, xylose, ribose, 2-deoxyribose, etc.) and hexoses (e.g., glucose, fructose, galactose, mannose, sorbose, rhamnose, fucose, etc.).. . .

DETD Examples of the above water-**soluble** disaccharides include maltose, cellobiose, .alpha.-trehalose, lactose, sucrose, etc. In particular, lactose and sucrose are preferred.

DETD Examples of the above water-**soluble** oligosaccharides include trisaccharides (e.g., maltotriose, raffinose, etc.) and tetrasaccharides (e.g., stachyose, etc.). In particular, trisaccharides are preferred.

DETD Examples of the above water-**soluble** polysaccharides include glucans such as cellulose, starch, glycogen, etc., galacturonan such as pectic acid, etc., mannuronan such as alginic acid,. . .

DETD Examples of the derivatives of the above water-**soluble** monosaccharides, disaccharides, oligosaccharides and polysaccharides include glucosamine, galactosamine, glucuronic acid, galacturonic acid, etc.

DETD Examples of the above water-**soluble** organic acids or salts thereof include citric acid, tartaric acid, malic acid, alkaline metal (e.g., sodium, potassium, etc.) salts thereof,. . .

DETD Examples of the above water-**soluble** amino acids include neutral amino acids such as glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, proline, hydroxyproline,. . . acids such as aspartic acid, glutamic acid, etc.; basic amino acids such as lysine, arginine, histidine, etc. Salts of these water-**soluble** amino acids with acids (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, etc.) or alkalis (e.g., alkaline metals such as sodium,. . .

DETD Examples of the water-**soluble** peptides, proteins or their derivatives include casein, globulin, prolamin, albumin, gelatin, etc.

DETD . . . above concentration by the total ionic valency. The osmotic pressure adjustor may be added so that their concentration exceeds their **solubility**, and a part of it may be dispersed.

DETD Initially, an amorphous water-**soluble** physiologically active substance is dispersed in a solution of a polymer in a water-insoluble

organic solvent, and the resulting dispersion. . .

DETD If the water-**soluble** physiologically active substance is available in amorphous form, it can be used as it is. Even if it is available in crystalline form, however, it can be used after making it amorphous. The amorphous water-**soluble** physiologically active substance is preferably obtained from an aqueous solution, preferably a dilute aqueous solution, of a water-**soluble** physiologically active substance by a rapid drying process such as freeze drying or spray drying. As described above, the amorphous water-**soluble** physiologically active substance is preferably used in the form of microparticles, and the average **particle size** of the physiologically active substance is generally about 1 nm to about 10 .mu.m, preferably about 1 nm to about. . .

DETD . . . homogenization, ultrasonication, etc. In this case, it is advantageous to use the above water-insoluble organic solvent in combination with a water-**soluble** organic solvent. The water-**soluble** organic solvent is not specifically limited so long as it is **soluble** in water and miscible with the above water-insoluble organic solvent. Examples of the water-**soluble** organic solvents include alcohols (e.g., methanol, ethanol, propyl alcohol, isopropyl alcohol, etc.), acetone, acetonitrile, etc. In the s/o type emulsions, it is preferred that the physiologically active substance be dispersed in the form of fine microparticles having an average **particle size** of about 1 nm to about 10 .mu.m, preferably about 1 nm to about 1 .mu.m.

DETD (1) An amorphous water-**soluble** physiologically active substance can be entrapped into the microcapsules more efficiently than in conventional processes such as the coacervation phase. . .

CLM What is claimed is:

1. A sustained-release microcapsule which is obtained by the steps comprising: selecting a dispersion of an amorphous water-**soluble** pharmaceutical agent having a **particle size** of from 1 nm-10 .mu.m in a solution of a polymer in an organic solvent, wherein said pharmaceutical agent is. . . from 0.001-90% (w/w) and said polymer has a wt. avg. molecular weight of from 2,000-800,000; dispersing said dispersion of amorphous water-**soluble** pharmaceutical agent in an aqueous phase to prepare an s/o/w emulsion; and subjecting the s/o/w emulsion to in-water drying.

12. The microcapsule according to claim 1, wherein the amorphous water-**soluble** pharmaceutical agent is obtained from an aqueous solution of a water-**soluble** pharmaceutical agent by a drying process.

14. The microcapsule according to claim 1, wherein the pharmaceutical agent is readily **soluble** in water.

15. The microcapsule according to claim 1, wherein the water-**solubility** of the pharmaceutical agent is not less than about 1 g/100 ml at 20.degree. C.

16. The microcapsule according to claim 1, wherein the water-**solubility** of the pharmaceutical agent is not less than about 5 g/100 ml at 20.degree. C.

17. The microcapsule according to claim 1, wherein the average **particle size** of the pharmaceutical agent is not more than about 1 .mu.m.

L7 ANSWER 19 OF 23 USPATFULL

AN 2000:117322 USPATFULL

TI Substained release microcapsule of physiologically active compound which is slightly water **soluble** at pH 6 to 8

IN Takada, Shigeyuki, Kobe, Japan
Nakagawa, Yasushi, Kawanishi, Japan
Iwasa, Susumu, Kyoto, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6113941 20000905
WO 9610397 19960411
AI US 1995-569097 19951222 (8)
WO 1995-JP1905 19950921
19961222 PCT 371 date
19961222 PCT 102(e) date
PRAI JP 1994-237948 19940930
DT Utility
FS Granted
EXNAM Primary Examiner: Bawa, Raj
LREP Fitzpatrick, Cella, Harper & Scinto
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 789
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A pharmaceutical preparation is provided by a microcapsule containing a physiologically active substance which is water-**soluble** only at a pH of about 3 or below, and a polymer which is biodegradable upon oral administration. A process for producing the microcapsule is also provided.

TI Substained release microcapsule of physiologically active compound which is slightly water **soluble** at pH 6 to 8

AB A pharmaceutical preparation is provided by a microcapsule containing a physiologically active substance which is water-**soluble** only at a pH of about 3 or below, and a polymer which is biodegradable upon oral administration. A process. . .

SUMM In general, drugs that are slightly water-**soluble** at pH 6 to 8 are slightly absorbed into the digestive tract after oral administration because of their low dissolution rates. In order to improve the **solubility** of the drugs, the slightly water-**soluble** drugs have been formulated as readily water-**soluble** salts, or a solution adjuvant is introduced as an additive. However, in the case of hydrochloric acid salts for example,. . . In addition, because the acid that is added as an additive readily dissolves and disappears, the effects of improving the **solubility** also disappear.

SUMM Pharmaceutical Research, Vol. 8, No. 1, p. 101 (1991) reports studies on nanocapsules which contain the slightly water-**soluble** drug indomethacin. However, indomethacin is not readily **soluble** in water at a pH no higher than 3. In addition, no improvement in the absorption of the drug has. . .

SUMM The present inventors have designed and studied a microcapsule containing a physiologically active substance that is **soluble** in water at a pH no higher than about 3 by using a biodegradable polymer as a base. As a. . . it has been found that a microcapsule prepared by adding to a biodegradable polymer a physiologically active substance that is water-**soluble** at a pH no higher than about 3 and dissolving the mixture in an organic solvent gradually releases a water-**soluble** low molecular weight free acid and the physiologically active substance at the same time after degradation of the base occurs in the digestive tract after oral administration. It has also been found that the microcapsule **solubilizes** a physiologically active substance that is normally insoluble in the digestive tract from the duodenum to the rectum, thereby improving. . .

SUMM The present invention provides a microcapsule comprising a physiologically active substance which is water-**soluble** at a pH no higher than about 3, and a biodegradable polymer.

SUMM . . . invention also provides a microcapsule which is obtainable by dissolving in an organic solvent a physiologically active substance which is water-**soluble** at a pH no higher than about 3 together

with a biodegradable polymer, and then subjecting the resulting solution to. . .

SUMM . . . to a process for producing a microcapsule which comprises dissolving in an organic solvent a physiologically active substance which is water-**soluble** at a pH no higher than about 3 together with a biodegradable polymer, and then subjecting the resulting solution to. . .

SUMM The present invention makes it possible to encapsulate a physiologically active substance which is water-**soluble** at a pH no higher than about 3 into microcapsules by using biodegradable polymers. Further, addition of an appropriate excipient. . .

SUMM The physiologically active substance to be used in the present invention is a drug which is readily **soluble** in water under acidic conditions, in particular at a pH no higher than about 3. Preferably, the physiologically active substance is slightly **soluble** in water under neutral conditions, in particular at pH 6 to 8. The term " **soluble** in water" or "water-**soluble**" used herein regarding the physiologically active substance means that the water-**solubility** of the physiologically active substance is not less than about 0.01 g, preferably not less than about 1 g, per 100 ml of water at about 20.degree. C. The term "slightly **soluble** in water" or "slightly water-**soluble**" used herein regarding the physiologically active substance means that the water-**solubility** of the physiologically active substance is not more than about 0.01 g, preferably not more than about 0.001 g, per. . .

SUMM Examples of the anti-platelet aggregation drugs include ticlopidine, **cilostazol**, alprostadil, limaprost, dipyridamole, ethyl icosapentaenoate, beraprost, ozagrel, aspirin, etc.

SUMM . . . polymer to be used in the present invention is a biocompatible polymer which is degradable in living bodies and slightly **soluble** or insoluble in water.

SUMM The aggregation-preventing agents include water-**soluble** inorganic salts, organic acids and organic acid salts. They are not specifically limited so long as they can be administered. . .

SUMM The water-**soluble** organic acids include, for example, citric acid, tartaric acid, malic acid, succinic acid, benzoic acid, chondroitin sulfate, dextran sulfate, carboxymethylcellulose,. . .

SUMM The water-**soluble** organic acid salts include, for example, salts of acetic acid, citric acid, tartaric acid, malic acid, succinic acid, benzoic acid,. . .

SUMM In particular, water-**soluble** inorganic salts are preferred. These water-**soluble** inorganic salts, organic acids and organic acid salts can be used alone or in combination thereof in an appropriate ratio.

SUMM The formulation ratio of the above water-**soluble** inorganic salt, organic acid or organic acid salt based on the polymer may be in the range in which aggregation-preventing. . .

SUMM (1) The microcapsules can improves absorption of a physiologically active substance which is slightly **soluble** and slightly absorbable into the digestive tract from the duodenum to the rectum. That is, the biodegradable polymer contained in. . . a base degrades in the digestive tract after administration of the microcapsules to gradually release a free acid of a water-**soluble** low molecular weight molecule (monomer to oligomer) together with a physiologically active substance. Thus, the physiologically active substance which does not normally dissolve in the digestive tract is **solubilized** by the released acid, and thus its absorption can be improved.

SUMM (2) Sustained release microcapsules particularly for oral administration can be prepared from a slightly water-**soluble** physiologically active substance by using a biodegradable polymer having varying biodegradation rates. Further, addition of an appropriate additive can control. . .

SUMM (3) When a readily **soluble** salt such as hydrochloric acid salt is used to improve the **solubility** of physiologically active

substances as in prior art techniques, hydrochloric acid separates from the hydrochloric acid salt during storage. However,. . .

SUMM (4) When additives such as acids are added as solution adjuvants, the acids readily dissolve and disappear and **solubilization** effects are not obtained. On the other hand, the **solubility** of the biodegradable polymers in the present invention can be controlled.

SUMM . . . process, phase separation process, spray drying process, etc. These processes can be controlled to provide homogeneously spherical microcapsules having a **particle size** of 0.1 to 1000 .mu.m.

DETD . . . of Compound A in 0.5% methylcellulose provided a low administration ratio of 5.4% because Compound A has a very low **solubility** at the pH in the small intestine, whereas the lactic acid/glycollic acid copolymer microcapsules increased the absorption ratio because they. . . lactic acid or glycollic acid together with the drug in the small intestine and the drug was, therefore, present in **solubilized** form. In addition, T.sub.max was prolonged six times, and the prolonged release was achieved.

CLM What is claimed is:

1. A sustained release pharmaceutical microcapsule comprising: a basic physiologically active compound which is **soluble** in 20.degree. water at a pH of about 3 or less but not more than about 0.01 g of said compound is **soluble** in 100 ml of 20.degree. C. water at pH to 8, wherein said basic physiologically active compound comprises a moiety. . .

7. The microcapsule according to claim 1, wherein the water-**solubility** of the physiologically active compound is not less than about 1 g/100 ml at 20.degree. C. and pH 3 or. . .

L7 ANSWER 20 OF 23 USPATFULL

AN 1999:128527 USPATFULL

TI Method of inducing vasorelaxation to treat pulmonary hypertension

IN Lawson, Charles A., Verona, NJ, United States
Pinsky, David J., Riverdale, NY, United States
Smerling, Arthur, New Rochelle, NY, United States
Stern, David M., Great Neck, NY, United States

PA The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)

PI US 5968911 19991019
WO 9509636 19950413

AI US 1997-362571 19970218 (8)
WO 1994-US11248 19941004
19970218 PCT 371 date
19970218 PCT 102(e) date

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DT Utility

FS Granted

EXNAM Primary Examiner: Kunz, Gary L.

LREP White, John P.Cooper & Dunham LLP

CLMN Number of Claims: 47

ECL Exemplary Claim: 1

DRWN 19 Drawing Figure(s); 31 Drawing Page(s)

LN.CNT 1790

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method of selectively decreasing pulmonary vascular resistance in a subject by administering endobronchially a drug chosen from among cAMP analogs, cGMP analogs, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs.

DRWD FIG. 10: Effect of inhalation of 8-Br-cGMP **solubilized** in DMSO.

DRWD FIG. 11: Percent change in SVR and PVR upon administration of dibutyryl-cAMP **solubilized** in DMSO (Thromboxane model).

DETD In another embodiment the administering comprises inhaling the drug in

an aerosol form. In a specific embodiment the aerosol **particle size** is between about 0.5 micrometers and about 10 micrometers.

DETD . . . one embodiment the aerosolized drug is administered as an aqueous solution. Preferably, the aerosolized drug is administered as a lipid **soluble** aqueous solution. In another embodiment the aerosolized drug is administered as a micronized powder.

DETD . . . - Indolidan (LY 195115), Cilostamide (OPC 3689), Lixazinone (RS 82856), Y-590, Imazodan (CI 914), SKF 94120, Quazinone, IC 153, 110, **Cilostazol** (OPC 13013), Bemorandan (RWJ 22867), Siguazodan (SK&F 94836), Adibendan (BM 14,478), Milrinone (WIN 47203), Enoximone (MDL 17043), Pimobendan (UD-CG 115,. . .

DETD . . . this effect can be enhanced by increasing the ability of 8-Br-cGMP to penetrate cell membranes. This has been done by **solubilizing** the 8-Br-cGMP in the solvent dimethyl sulfoxide (DMSO), with similar administration as above. When 8-Br-cGMP is mixed in this way. . .

DETD Dibutyryl cAMP **solubilized** in DMSO was administered in the thromboxane model. Dibutyryl cAMP caused a 20% drop in PVR with little effect on. . .

DETD . . . hypertension (2,3). Rationale for the use of nitric oxide to treat pulmonary hypertension is based upon its ability to stimulate **soluble** guanylyl cyclase found in smooth muscle cells throughout the vasculature, leading to an increase in intracellular cGMP and subsequent vasodilation. . .

DETD To overcome these limitations, it was hypothesized that administration of a stable lipid **soluble** analog of cGMP (8-Br-cGMP) might have similar beneficial pulmonary vasodilating effects. In isolated lung models, this agent administered intravenously effectively. . .

DETD . . . pulmonary hypertension..sup.2,3 Rationale for the use of nitric oxide to treat pulmonary hypertension is based upon its ability to stimulate **soluble** guanylate cyclase found in smooth muscle cells throughout the vasculature, leading to an increase in intracellular cGMP and subsequent vasodilation..sup.24. . .

L7 ANSWER 21 OF 23 USPATFULL

AN 1998:57976 USPATFULL

TI Medical material and process for producing the same

IN Iguchi, Seiichiro, Tokushima, Japan
Higashino, Rika, Tokushima, Japan

PA Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan (non-U.S. corporation)
Otsuka Pahrmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)

PI US 5756553 19980526
WO 9503075 19950202

AI US 1995-403828 19950321 (8)
WO 1995-JP9401162 19950713
19950321 PCT 371 date
19950321 PCT 102(e) date

PRAI JP 1993-180300 19930721

DT Utility

FS Granted

EXNAM Primary Examiner: Azpuru, Carlos A.

LREP Sughrue, Mion, Zinn, Macpeak & Seas, PLLC

CLMN Number of Claims: 31

ECL Exemplary Claim: 1

DRWN 8 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 874

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A medical material of the present invention comprises a polymer or copolymer of a vinyl derivative having a polar group, said polymer or copolymer containing an antiplatelet agent. Since the antiplatelet agent can be continuously dissolved in the active concentration, the material has high anticoagulant activity and inhibition action of platelet loss due to activation of platelet.

SUMM . . . and polymer materials. As a result, it has been found that it is possible to formulate an antiplatelet agent, particularly **cilostazol**, dipyridamole or aspirin in a polymer or copolymer of a vinyl derivative having a polar group, and that a release. . .

DETD Examples of the antiplatelet agent include **cilostazol**, dipyridamole, aspirin, ticlopidine, beraprost, indomethacin, sulfinpyrazone, satigrel, d-indobufen, dazoxiben, furegrelate, ozagrel, pirmagrel, dazmegrel, midazogrel, daltroban, sulotroban, vapiprost, clopidgrel, prostaglandin E.sub.1,. . . [1.alpha.,2.alpha.(Z), 3.beta.,4.alpha.]-(.+-.)-7-{3[(phenylsulfonyl)amino]-bicyclo [2,2,1] hept-2-yl}-5-heptenoic acid, (-)-cis-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-dibenzothiazepine-4-(5H)-one and the like. They can be used alone or in combination thereof. Among them, **cilostazol**, dipyridamole, beraprost, satigrel and aspirin can be suitably used. Particularly, **cilostazol** is preferred.

DETD . . . methylene chloride or chloroform is preferable to poly(methyl methacrylate), because the solvent can be easily distilled off and has high **solubility**.

DETD In the present invention, a particularly preferred combination is that of **cilostazol** as the antiplatelet agent and an ethylene-vinyl alcohol copolymer. Since **cilostazol** is superior in compatibility with the ethylene-vinyl alcohol copolymer, **cilostazol** can be uniformly dispersed. Also, **cilostazol** can be uniformly dispersed in soft polyvinyl chloride by adjusting the blending of additives.

DETD . . . include a tube having a three-layer structure wherein an ethylene-.alpha.-olefin copolymer elastomer layer, a maleic acid-modified polyethylene layer and a **cilostazol**-containing ethylene-vinyl alcohol copolymer layer are laminated in order from the outer layer. On the other hand, those which are molded. . .

DETD . . . used for a peripheral circulation circuit during cardiopulmonary bypass, not only anticoagulant action but angiectatic action is developed by using **cilostazol** or dipyridamole as the antiplatelet agent to be blended. Therefore, circulatory failure of distal tissue caused by controlled shock can. . .

DETD . . . present invention can be suitably used as it is or after knitting, as a vascular stent. In this case, when **cilostazol** is used as the antiplatelet agent, not only thrombogenesis at the surface of the stent but endothelial proliferation of blood. . .

DETD . . . stabilizer (mixture of calcium stearate and zinc stearate) and 0.1 parts by weight of a lubricant] and 10 mg of **cilostazol** were dissolved in 5 ml of tetrahydrofuran and the resulting solution was casted on a glass plate, which was allowed. . . for 5 hours under reduced pressure (-760 mmHg) to distill off tetrahydrofuran to give a transparent film. The amount of **cilostazol** for the resulting film was 5% by weight.

DETD . . . 10 hours under reduced pressure (-760 mmHg), instead of distilling off tetrahydrofuran, a white film was obtained. The amount of **cilostazol** for the resulting film was 5% by weight.

DETD . . . 37.degree. C. for one hour. Thereafter, this operation was repeated for 8 hours to determine a variation with time in **cilostazol** concentration in a dissolution solution. The results are shown in FIG. 1.

DETD As is apparent from FIG. 1, continuous dissolution of **cilostazol** in the concentration exceeding the effective concentration (1.1 .mu.g/ml) is observed in all of films of Examples 1, 2 and. . .

DETD . . . removing method of solvent between Examples 1 and 2. Therefore, it is found that a difference in dissolution concentration of **cilostazol** observed is caused by the above difference, which results in difference in release properties.

DETD . . . dissolution of the plasticizer was observed in all Examples. As a result, it was confirmed that selective dissolution (release) of **cilostazol** can be conducted.

DETD . . . film was produced according to the same manner as that described in Example 1 except for changing the amount of **cilostazol** for the film of polyvinyl chloride to 10% by weight. As a result, the resulting film was cloudy. It is considered that this is because **cilostazol** is contained in the amount exceeding the amount which causes a saturated state. Regarding the resulting film, the dissolution amount of **cilostazol** was examined according to the same manner as that described above. As a result, dissolution in the concentration exceeding the. . .

DETD Further, when the amount of the plasticizer was increased, the resulting film became cloudy in the lower amount of **cilostazol**. In addition, when the resulting film is transparent and the amount of **cilostazol** is the same, the larger the amount of the plasticizer, the higher the dissolution concentration. Even if the polymerization degree of polyvinyl chloride to be used is varied, the amount of **cilostazol** which causes formation of the cloudy film is scarcely influenced.

DETD . . . Chemical Industry Co., Ltd.), ethylene content: 32 molar %) was molten with heating on a hot plate at 180.degree. C., **cilostazol** was added thereto. Immediately after that, the melt was kneaded with stirring and the resulting mixture was pressed by a pressing machine to give a film having a thickness of about 100 .mu.m. The amount of **cilostazol** for the resulting film was 10% by weight.

DETD . . . as that described in Example 4 except for using 475 mg of an ethylene-vinyl alcohol copolymer and 25 mg of **cilostazol**, a film was obtained.

DETD . . . to the same manner as that described in Examples 1, 2 and 3 to determine a variation with time in **cilostazol** concentration in a dissolution solution. The results are shown in FIG. 2.

DETD As is apparent from FIG. 2, gentle decrease of the dissolution amount is observed, however, sustained release of **cilostazol** in the concentration exceeding the effective concentration (1.1 .mu.g/ml) until 8 hours after the beginning of dissolution is observed. Accordingly,. . . films of Examples 4 and 5 have high anticoagulant activity. Further, it is found that, the larger the amount of **cilostazol** (Example 4), the higher the dissolution concentration.

DETD In Example 4, a transparent film could be obtained even if the amount of **cilostazol** was increased, until the amount reaches 20% by weight. However, when the amount exceeds 30% by weight, a cloudy film was obtained. Further, the dissolution amount of **cilostazol** was determined according to the same manner as that described above. As a result, dissolution of **cilostazol** in the amount exceeding the effective concentration was observed from the beginning to 8 hours after that in all films. However, regarding the cloudy film, the dissolution concentration exceeding that of the transparent film containing 20% by weight of **cilostazol** is not observed. Even if a kind of the ethylene-vinyl alcohol copolymer (e.g. ethylene content, molecular weight, saponification degree, etc.) was varied, the amount of **cilostazol** which causes formation of the cloudy film was scarcely influenced.

DETD . . . weight of polyvinyl chloride having an average degree of polymerization of 1100 and 40 parts by weight of DOP) and **cilostazol** (contained in an amount of 5% by weight to a total solid content) in tetrahydrofuran (total concentration: 4% by weight). . .

DETD . . . solution of an ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd., ethylene content: 32 molar %) and **cilostazol** (contained in an amount of 10% by weight to a total solid content) in 1,1,1,3,3,3-hexafluoro-2-propanol (total concentration: 5% by weight). . .

DETD . . . prosthesis 1, pipes 5 and 6 for circulation are connected, respectively. The solution 4 of the ethylene-vinyl alcohol copolymer and **cilostazol** is circulated in the vascular prosthesis 1 using a pump 3 to coat the blood vessel.

DETD . . . weight of polyvinyl chloride having an average degree of polymerization of 1100 and 40 parts by weight of DOP) and **cilostazol** (contained in an amount of 5% by weight to a total solid content) in tetrahydrofuran (total concentration: 10% by weight). . .

DETD . . . a stabilizer (mixture of calcium stearate and zinc stearate) and 0.2 parts by weight of a lubricant] was mixed with **cilostazol** in the melting condition at a proportion of 5% by weight of **cilostazol** to the total amount. By using the above soft polyvinyl chloride containing **cilostazol** and soft polyvinyl chloride [comprising 100 parts by weight of polyvinyl chloride having an average degree of polymerization of 1700,. . . atmosphere. The resulting tube was composed of a soft polyvinyl chloride layer(thickness: 1.00 mm) as an outer layer and a **cilostazol** -containing soft polyvinyl chloride layer(thickness: 0.25 mm) as an inner layer.

DETD . . . ethylene-vinyl alcohol copolymer (ethylene content: 32 molar %, manufactured by Nippon Synthetic Chemical Industry Co., Ltd.) and 40 mg of **cilostazol** were dissolved in 10 ml of 1,1,1,3,3,3-hexafluoro-2-propanol and the resulting solution was casted on a glass plate, which was dried. . . vacuum drier at 40.degree. C. for 24 hours to give a transparent film (thickness: about 50 .mu.m). The amount of **cilostazol** of the resulting film was 10% by weight.

DETD . . . according to the same manner as that described in Example 1, 2 and 3. As a result, continuous release of **cilostazol** in the concentration exceeding the effective concentration was observed, similar to those obtained in Examples 4 and 5.

DETD In this production process, a cloudy film was obtained when the amount of **cilostazol** exceeds 20% by weight.

DETD 360 Mg of poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company, Ltd.) and 40 mg of **cilostazol** were dissolved in 10 ml of chloroform and the resulting solution was casted on a glass plate, which was dried. . .

DETD . . . Industry Co., Ltd, ethylene content: 44 molar %) was pulverized by a chemical mill(model R-8) to collect particles having a **particle size** of 50 to 125 .mu.m. 900 Mg of the resulting particles were mixed with 100 mg of dipyridamole and the. . .

DETD Poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company Ltd.) was pulverized by a chemical mill(model R-8) to collect particles having a **particle size** of 50 to 125 .mu.m. 950 Mg of the resulting particles were mixed with 50 mg of dipyridamole and the. . .

DETD . . . of the drug as well as a relation between the kind of the resin and release properties of the drug, **cilostazol** and dipyridamole showed same tendency.

DETD . . . drug as well as a relation between the kind of the resin and release properties of the drug, aspirin and **cilostazol** showed same tendency.

DETD 500 Mg of a Palmaz-Shatz stent (manufactured by Johnson & Johnson Co., U.S.A.) was dipped in an ethylene-vinyl alcohol copolymer-**cilostazol** solution [prepared by dissolving 500 mg of an ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd., Soarnol K3825N) and 500 mg of **cilostazol** in 100 ml of hexafluoro-2-propanol, amount of **cilostazol**: 50% by weight] and, after air-drying, the stent was dipped and air-dried again. This operation was repeated to produce a coating layer (amount of **cilostazol**: 50 % by weight) having a thickness of about 50 .mu.m. The resulting coated stent was dried at 40.degree. C. for 72 hours under vacuum to remove the solvent completely. Thereafter, it was dipped in an ethylene-vinyl alcohol copolymer-**cilostazol** solution [newly prepared by dissolving 950 mg of an ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd., Soarnol K3825N) and 50 mg of

cilostazol in 100 ml of 1,1,1,3,3,3-hexafluoro-2-propanol] and then air-dried. This operation was repeated to produce a second coating layer (amount of **cilostazol**: 5% by weight) on the above coating layer.

DETD . . . 44 molar %) was pulverized by a pulverizer (manufactured by Fritsch Co., rotor speed mill) to collect particles having a **particle size** of 50 to 125 .mu.m. Then, 45 g of the particles were dryblended with 5 g of **cilostazol** (manufactured by Otsuka Pharmaceutical Co., Ltd.) and the mixture was extruded with kneading at 180.degree. C. under a nitrogen atmosphere. . . the extrudate was stretched to produce an ethylene-vinyl alcohol copolymer filament having a size of 0.25 .mu.m in diameter, wherein **cilostazol** is uniformly dispersed. The amount of **cilostazol** in the resulting copolymer filament was 10% by weight.

DETD 1.8 G of poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company Ltd.) and 0.2 g of **cilostazol** (manufactured by Otsuka Pharmaceutical Co., Ltd.) were dissolved in 100 ml of chloroform. The resulting solution was coated on the. . .

DETD . . . Ltd.) was pulverized by a pulverizer (manufactured by Fritsch Co., rotor speed mill) and screened to collect particles having a **particle size** of 50 to 125 .mu.m. Then, 95 g of the particles were dryblended with 5 g of **cilostazol** and the blend was extruded with kneading at 180.degree. C. under a nitrogen atmosphere by an extruder (manufactured by CSI. . .

CLM What is claimed is:

. . . group as a part thereof, wherein said material uniformly contains therein an antiplatelet agent selected from the group consisting of **cilostazol**, dipyridamole and satigrel.

. . . medical material according to claim 1, wherein the antiplatelet agent is at least one selected from the group consisting of **cilostazol** , dipyridamole, and satigrel.

. . . or copolymer of a vinyl derivative having a polar group as a part thereof, wherein said material uniformly contains therein **cilostazol**.

14. The medical material according to claim 13, wherein the amount of **cilostazol** is 0.01 to 60 parts by weight based on 100 parts by weight of the medical material.

15. The medical material according to claim 14, wherein the amount of **cilostazol** is 1 to 44.4 parts by weight based on 100 parts by weight of the medical material.

16. The medical material according to claim 15, wherein the amount of **cilostazol** is 4.8 to 33.3 parts by weight based on 100 parts by weight of the medical material.

17. The medical material according to claim 13, wherein the amount of **cilostazol** is not more than 20% by weight based on the total weight.

20. The medical material according to claim 19, wherein the material contains therein **cilostazol**.

21. The medical material according to claim 20, wherein the amount of **cilostazol** is not more than 20% by weight based on the total weight of the material.

. . . A medical material wherein a polymer or copolymer of a vinyl derivative having a polar group as part thereof and **cilostazol** are mixed in a molten state.

. . . vinyl derivative having a polar group as a part thereof with an antiplatelet agent selected from the group consisting of **cilostazol**, dipyridamole and satigrel in a molten state.

. . . vinyl derivative having a polar group as a part thereof and an antiplatelet agent selected from the group consisting of **cilostazol**, dipyridamole and satigrel in a solvent and then removing the solvent.

28. A process for producing the medical material of claim 24 or 25, wherein the antiplatelet agent is **cilostazol**.

29. The process for producing a medical material according to claim 27, wherein the antiplatelet agent is **cilostazol**.

L7 ANSWER 22 OF 23 DRUGU COPYRIGHT 2002 THOMSON DERWENT
AN 1998-34828 DRUGU P G
TI Biopharmaceutical considerations in preparing dosage forms of highly lipophyllic compounds for 14C tracer studies in humans.
AU Bramer S L; Yalkowsky H; Tesconi M S
CS Otsuka; Univ.Arizona
LO Rockville, Md.; Tucson, Ariz., USA
SO Pharm.Res. (14, No. 11, Suppl., S612, 1997)
CODEN: PHREEB ISSN: 0724-8741
AV Otsuka America Pharmaceuticals, Inc., Rockville, MD 20850, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The clinical impact of **particle size** when preparing dosage forms of highly lipophilic compounds (OPC-13013, **cilostazol**) for 14-C tracer studies in humans was investigated in-vivo and in-vitro. The results demonstrate that **particle size** is of concern when preparing dosage forms for 14C tracer studies. Particular attention should be taken with highly insoluble compounds, especially when a solution is not an option, and **solubilization** and re-crystallization techniques may avoid these **particle size** differences. (conference abstract).
AB The clinical impact of **particle size** when preparing dosage forms of highly lipophilic compounds (OPC-13013, **cilostazol**) for 14-C tracer studies in humans was investigated in-vivo and in-vitro. The results demonstrate that **particle size** is of concern when preparing dosage forms for 14C tracer studies. Particular attention should be taken with highly insoluble compounds, especially when a solution is not an option, and **solubilization** and re-crystallization techniques may avoid these **particle size** differences. (conference abstract).
ABEX. . . 4 times larger than crystals of the unlabeled powder. The unmilled labeled drug dissolved at a slower rate. Standardization of **particle size** of labeled and unlabeled drug resulted in identical dissolution profiles. The clinical study was repeated with a solution avoiding these. . .
CT [01] **CILOSTAZOL** *OC; **CILOSTAZOL** *DM; CILOSTAZO *RN; IN-VIVO *FT; IN-VITRO *FT; PHARM.PREP. *FT; PHARMACEUTICS *FT; BLOOD-PLASMA *FT; CONC. *FT; BIOAVAILABILITY *FT; DISSOLUTION *FT; ANTIAGGREGANTS. . .
RN [01] **73963-72-1**

L7 ANSWER 23 OF 23 USPATFULL
AN 93:48526 USPATFULL
TI Platelet aggregation inhibitory agents
IN Gollamudi, Ramachander, Memphis, TN, United States

Feng, Zixia, Memphis, TN, United States
PA Research Corporation Technologies, Inc., Tucson, AZ, United States (U.S. corporation)
PI US 5219867 19930615
AI US 1992-927684 19920810 (7)
RLI Continuation-in-part of Ser. No. US 1991-808000, filed on 16 Dec 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner: Hydorn, Michael B.
LREP Scully, Scott, Murphy & Presser
CLMN Number of Claims: 84
ECL Exemplary Claim: 1
DRWN 22 Drawing Figure(s); 16 Drawing Page(s)
LN.CNT 1556
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to substantially pure stereoisomers of a compound of the formula: ##STR1## wherein n.sub.1 and n.sub.2 are the same or different and are 1 or 2; X is alkyl (C.sub.1 -C.sub.10), aryl (C.sub.6 -C.sub.10) or aralkyl (C.sub.7 -C.sub.12); and wherein R, R.sub.1, R.sub.2 and R.sub.3 are the same or different and are chosen from H, alkyl (C.sub.1 -C.sub.10), aryl (C.sub.6 -C.sub.10), aralkyl (C.sub.7 -C.sub.12), or a heterocyclic group, and addition salts thereof with pharmaceutically acceptable acids. The invention also relates to a method for the inhibition of blood platelet aggregation in a blood supply comprising administering to said blood supply a blood platelet aggregation inhibiting amount of the compounds of the present invention.
SUMM 10. Miscellaneous structures: e.g. amipizone, **cilostazol**, ticlopidine, bencyclane, picotamide, etc.
SUMM . . . (c) thromboxane A.sub.2 antagonists; (d) prostacyclin activator: nafazatrom; or (2) inhibition of arachidonic acid-independent aggregation: (a) cyclic AMP phosphodiesterase inhibitors; **cilostazol**, and pyrimidine derivatives; (b) adenylate cyclase activators; prostaglandins and ticlopidine.
DETD The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water **soluble**) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form. . . can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required **particle size** in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be. . .

=> file home

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	113.22	119.77

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.62	-0.62

FILE 'HOME' ENTERED AT 10:52:10 ON 07 OCT 2002

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